Is there a role for bone tissue in osteoarthritis?

Osteoarthritis (OA) is a major health burden in our ageing societies. Our comprehension of this complex musculoskeletal disease has shifted from one affecting a single tissue, the articular cartilage, to a whole organ failure that affects different tissues including bone and the synovial membrane. This disease affects more women than men, yet we still do not know the underlying causes of this discrepancy. Indeed, a number of factors are involved in OA pathophysiology and progression. However, in recent years the key role played by the subchondral bone tissue in OA has been underscored, yet mechanisms leading to this still remain unknown. This article explores how bone and, in particular, the subchondral bone tissue is modified in OA, and which mechanisms could be responsible for the alterations observed.

KEYWORDS: bone/cartilage cross-talk ■ bone marrow lesions ■ mineralization ■ osteoarthritis ■ subchondral bone

Daniel Lajeunesse

Département de Medicine, CRCHUM, Hôpital Notre-Dame, 1560, Rue Sherbrooke Est, Montréal, Québec, H2L 4M1, Canada
Tel.: +1 514 890 8000
Fax: +1 514 412 7583
daniel.lajeunesse@umontreal.ca

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 now 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

future medicine part of fsg

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 E_2 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 fibrillation 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

limbs. Notwithstanding the adjustment for misalignment, bone marrow edema lesions were still strongly associated with radiographic progression. BMLs are also associated with poorly mineralized sclerotic bone tissue in OA patients [8]. This increased, undermineralized osteoid matrix is due to an increase of the ratio of α1 to α2 chains in OA compared with normal tissue [61,62,72,73]; a situation we and others also observed in human OA osteoblasts *in vitro* [74] and which was linked with elevated TGF-β1 levels in these cells [27,74]. The control of skeletal patterning and tissue remodeling involves a number of signaling molecules, and in particular, members of the bone morphogenetic protein, TGF-β superfamily and Wnts [75–84]. A potential role for Wnts in OA pathophysiology has been proposed based on elevated circulating Dickkopf-related protein 1 (DKK1) levels in hip OA patients that corresponded to OA grade [85], therefore implying that reduced Wnt/β-catenin signaling would be present in OA since DKK1 is an antagonist of this pathway [86,87]. The low-density lipoprotein receptor-related protein (LRP)5 locus on chromosome 11q was recently associated with OA susceptibility following genome-wide scans. Mutations of *LRP5* have previously been associated with abnormal bone mass regulation and could be the cause of the abnormal bone tissue mineralization and remodeling observed in OA patients. Although no individual polymorphisms were found in a study of 187 individuals, an altered haplotype of LRP5 was identified that increases the risk of OA by 1.6-times [88]. Zhu *et al.* recently demonstrated a key role of both increases [89] and decreases [90] of the Wnt canonical β-catenin pathway in mouse cartilage in the development of OA-like features. Hence, whether the Wnt/β-catenin signaling pathway is involved in OA will need more substantial evidence both from basic science and clinical studies. In addition, although LRP5 has been exclusively associated with the canonical Wnt/β-catenin signaling pathway in bone, recent studies also suggest that it could be involved with a skeletal role of gut-derived serotonin signaling in osteoblasts, osteocytes and osteoclasts [91,92]. If demonstrated in OA, this could be very attractive as serotonin mediates central and peripheral effects that could be linked with bone remodeling, which is altered in OA.

Hypotheses to explain the role of bone in OA have been proposed. Indeed, an inappropriate attempt to form and/or repair the subchondral bone tissue could lead to altered cartilage remodeling/degeneration and synovitis [93]. Since an increased BMI in OA patients is a risk factor, it was also proposed that OA could be a systemic disorder of stromal cell differentiation and lipid metabolism [94]. Recent observations of BMLs in OA [95–97], the increased risk of BMLs in the presence of dietary saturated lipid levels [10], and the fact that bone marrow cells show a deficit of chondrocytes and adipocytes yet increased osteogenesis would support this view [98]. In addition, the fact that leptin levels are high in the synovial fluid and sera of patients also agrees with a role of abnormal lipid metabolism [99–101]. Lately, Aspden proposed yet another hypothesis, in which OA would be a pathological growth, not decay, problem with excessive and poorly regulated growth of musculoskeletal tissues [50]. Cells would revert to an abnormal developmental phenotype with a loss of proper function such that tissue integrity could never be attained. The observation that OA osteoblasts grow at a faster rate than normal cells [30], their reported increased rate of proliferation [102] or their reduced apoptosis [102,103] would support this hypothesis. The abnormal phenotype of OA osteoblasts, as observed in a number of studies [27,28,30–32], also indicates abnormal development of these cells, with the ultimate differentiation parameter, namely mineralization, never fully attained in OA bone tissue [61,62,72]. This abnormal mineralization was also observed *in vitro* and was linked with abnormal type 1 collagen production in response to elevated TGF-β1 levels in these cells [74]. Moreover, abnormal responses to parathyroid hormone, prostaglandin E_2, IGF-1 and TGF-β1 have all been observed in OA osteoblasts, also suggesting an abnormal development of these cells, yet we still do not have any clues as to why the response to growth factors, hormones or eicosanoids is altered in these cells. Hence, the latter hypothesis is very attractive and deserves careful consideration.

Recent evidence also links leptin with OA pathophysiology [99,100,104], again supporting a hypothesis proposed by Aspden [94]. Here, centrally controlled bone resorption via leptin, an adipocytokine produced by adipocytes, and local modulation by adrenergic β2 receptors in osteoblasts [105,106], would be altered in OA. In addition, local leptin production by OA osteoblasts [102] could affect both osteoblasts and chondrocytes, whereas leptin production by chondrocytes would also affect chondrocytes via autocrine/paracrine interactions [104]. In addition, a recent study clearly showed that a link exists between leptin responsiveness of chondrocytes and BMI in OA patients [107]. This would, in turn, suggest that not all OA patients may

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 α1 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 [30,112]. 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 [130]. 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 alter 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 [44,152], 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 photobleaching [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

1 Lohmander LS: Articular cartilage and osteoarthrosis. The role of molecular markers to monitor breakdown, repair and disease. *J. Anat.* 184, 477–492 (1994).

2 Hamerman D: The biology of osteoarthritis. *N. Engl. J. Med.* 320, 1322–1330 (1989).

3 Poole RA: Cartilage in health and disease. In: *Arthritis and Allied Conditions: A Textbook of Rheumatology.* McCarty DJ, Koopman WJ (Eds). Lea and Febiger, PA, USA, 279–335 (1993).

4 Dieppe P, Cushnaghan J, Young P, Kirwan J: Prediction of the progression of joint space narrowing in osteoarthritis of the knee by bone scintigraphy. *Ann. Rheum. Dis.* 52, 557–563 (1993).

5 Wluka AE, Hanna F, Davies-Tuck M *et al.*: Bone marrow lesions predict increase in knee cartilage defects and loss of cartilage volume in middle-aged women without knee pain over 2 years. *Ann. Rheum. Dis.* 68, 850–855 (2009).

- **Among the first studies to describe a role of bone marrow lesions in osteoarthritis (OA) initiation.**

6 Roemer FW, Guermazi A, Javaid MK *et al.*: Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. *Ann. Rheum. Dis.* 68, 1461–1465 (2009).

7 Eckstein F, Benichou O, Wirth W *et al.*: Magnetic resonance imaging-based cartilage loss in painful contralateral knees with and without radiographic joint space narrowing: Data from the osteoarthritis initiative. *Arthritis Rheum.* 61, 1218–1225 (2009).

8 Hunter DJ, Gerstenfeld L, Bishop G *et al.*: Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. *Arthritis Res. Ther.* 11(1), R11 (2009).

- **First comprehensive MRI study that describes an alteration of OA bone tissue mineralization *in situ*.**

9 Davis MA: Epidemiology of osteoarthritis. *Clin. Geriatr. Med.* 4, 241–255 (1988).

10 Wang Y, Davies-Tuck ML, Wluka AE *et al.*: Dietary fatty acid intake affects the risk of developing bone marrow lesions in healthy middle-aged adults without clinical knee osteoarthritis: a prospective cohort study. *Arthritis Res. Ther.* 11, R63 (2009).

11 Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF: Obesity and knee osteoarthritis. *Ann. Intern. Med.* 109, 18–24 (1988).

12 Felson DT: The epidemiology of knee osteoarthritis: results from the Framingham osteoarthritis study. *Semin. Arthritis Rheum.* 20(Suppl. 1), 42–50 (1990).

13 Hochberg MC: Epidemiology of osteoarthritis: current concepts and new insights. *J. Rheumatol. Suppl.* 27, 4–6 (1991).

14 Carlson CS, Loeser RF, Jayo MJ, Weaver DS, Adams MR, Jerome CP: Osteoarthritis in cynomolgus macaques: a primate model of naturally occurring disease. *J. Orthop. Res.* 12, 331–339 (1994).

15 Carlson CS, Loeser RF, Purser CB, Gardin JF, Jerome CP: Osteoarthritis in cynomolgus macaques. III: effects of age, gender, and subchondral bone thickness on the severity of disease. *J. Bone Miner. Res.* 11, 1209–1217 (1996).

16 Dedrick DK, Goldstein SA, Brandt KD, O'Connor BL, Goulet RW, Albrecht M: A longitudinal study of subchondral plate and trabecular bone in cruciate-deficient dogs with osteoarthritis followed up for 54 months. *Arthritis Rheum.* 36, 1460–1467 (1993).

17 Yang C, Wolf E, Roser K, Delling G, Muller PK: Selenium deficiency and fulvic acid supplementation induces fibrosis of cartilage and disturbs subchondral ossification in knee joints of mice: an animal model study of Kashin-Beck disease. *Virchows Arch.* 423, 483–491 (1993).

18 Vener MJ, Thompson RC Jr, Lewis JL, Oegema TR Jr: Subchondral damage after acute transarticular loading: an *in vitro* model of joint injury. *J. Orthop. Res.* 10, 759–765 (1992).

19 Oettmeier R, Arokoski J, Roth AJ, Helminen HJ, Tammi M, Abendroth K: Quantitative study of articular cartilage and subchondral bone remodeling in the knee joint of dogs after strenuous training. *J. Bone Miner. Res.* 7(Suppl. 2), S419–S424 (1992).

20 Brandt KD, Myers SL, Burr D, Albrecht M: Osteoarthritic changes in canine articular cartilage, subchondral bone, and synovium fifty-four months after transection of the anterior cruciate ligament. *Arthritis Rheum.* 34, 1560–1570 (1991).

21 Sowers M, Zobel D, Weissfeld L, Hawthorne VM, Carman W: Progression of osteoarthritis of the hand and metacarpal bone loss. A twenty-year follow-up of incident cases. *Arthritis Rheum.* 34, 36–42 (1991).

22 Seibel MJ, Duncan A, Robins SP: Urinary hydroxy-pyridinium crosslinks provide indices of cartilage and bone involvement in arthritic diseases. *J. Rheumatol.* 16, 964–970 (1989).

23 Gregory JS, Waarsing JH, Day J *et al.*: Early identification of radiographic osteoarthritis of the hip using an active shape model to quantify changes in bone morphometric features: can hip shape tell us anything about the progression of osteoarthritis? *Arthritis Rheum.* 56, 3634–3643 (2007).

24 Raynauld JP, Martel-Pelletier J, Berthiaume MJ *et al.*: Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. *Arthritis Res. Ther.* 8, R21 (2006).

25 Pelletier JP, Raynauld JP, Berthiaume MJ *et al.*: Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. *Arthritis Res. Ther.* 9, R74 (2007).

26 McQueen FM, Gao A, Ostergaard M *et al.*: High-grade MRI bone oedema is common within the surgical field in rheumatoid arthritis patients undergoing joint replacement and is associated with osteitis in subchondral bone. *Ann. Rheum. Dis.* 66, 1581–1587 (2007).

27 Massicotte F, Lajeunesse D, Benderdour M *et al.*: Can altered production of interleukin-1β, interleukin-6, transforming growth factor-β and prostaglandin E_2 by isolated human subchondral osteoblasts identify two subgroups of osteoarthritic patients. *Osteoarthr. Cartil.* 10, 491–500 (2002).

28 Paredes Y, Massicotte F, Pelletier JP, Martel-Pelletier J, Laufer S, Lajeunesse D: Study of role of leukotriene B4 in abnormal function of human subchondral osteoarthritis osteoblasts. Effects of cyclooxygenase and/or 5-lipoxygenase inhibition. *Arthritis Rheum.* 46, 1804–1812 (2002).

29 Tardif G, Pelletier JP, Dupuis M, Geng C, Cloutier JM, Martel-Pelletier J: Collagenase 3 production by human osteoarthritic chondrocytes in response to growth factors and cytokines is a function of the physiological state of the cells. *Arthritis Rheum.* 42, 1147–1158 (1999).

30 Hilal G, Martel-Pelletier J, Pelletier JP, Ranger P, Lajeunesse D: Osteoblast-like cells from human subchondral osteoarthritic bone demonstrate an altered phenotype *in vitro*: possible role in subchondral bone sclerosis. *Arthritis Rheum.* 41, 891–899 (1998).

31 Sanchez C, Deberg MA, Piccardi N, Msika P, Reginster JY, Henrotin YE: Subchondral bone osteoblasts induce phenotypic changes in human osteoarthritic chondrocytes. *Osteoarthr. Cartil.* 13, 988–997 (2005).

▪ **Interesting study that identified the mechanisms behind cartilage loss induced by bone-derived putative factor(s).**

32 Sanchez C, Deberg MA, Piccardi N, Msika P, Reginster JY, Henrotin YE: Osteoblasts from the sclerotic subchondral bone downregulate aggrecan but upregulate metalloproteinases expression by chondrocytes. This effect is mimicked by interleukin-6, -1β and oncostatin M pre-treated nonsclerotic osteoblasts. *Osteoarthr. Cartil.* 13, 979–987 (2005).

▪ **Interesting study that identified the mechanisms behind cartilage loss induced by bone-derived putative factor(s).**

33 Bettica P, Cline G, Hart DJ, Meyer J, Spector TD: Evidence for increased bone resorption in patients with progressive knee osteoarthritis: longitudinal results from the Chingford study. *Arthritis Rheum.* 46, 3178–3184 (2002).

34 Kadri A, Funck-Brentano T, Lin H *et al.*: Inhibition of bone resorption blunts osteoarthritis in mice with high bone remodelling. *Ann. Rheum. Dis.* 69(8), 1533–1538 (2010).

35 Ding M, Odgaard A, Hvid I: Changes in the three-dimensional microstructure of human tibial cancellous bone in early osteoarthritis. *J. Bone Joint Surg. Br.* 85, 906–912 (2003).

36 Ding M, Danielsen CC, Hvid I: Bone density does not reflect mechanical properties in early-stage arthrosis. *Acta Orthop. Scand.* 72, 181–185 (2001).

37 Burr DB, Schaffler MB: The involvement of subchondral mineralized tissues in osteoarthrosis: quantitative microscopic evidence. *Microsc. Res. Tech.* 37, 343–357 (1997).

38 Foss MVL, Byers PD: Bone density, osteoarthrosis of the hip and fracture of the upper end of the femur. *Ann. Rheum. Dis.* 31, 259–264 (1972).

39 Roh YS, Dequeker J, Muiler JC: Bone mass is osteoarthrosis, measured *in vivo* by photon absorption. *J. Bone Joint Surg. Am.* 54A, 587–591 (1974).

40 Carlsson A, Nillson BE, Westlin NE: Bone mass in primary coxarthrosis. *Acta Orthop. Scand.* 50, 187–189 (1979).

41 Moore RJ, Fazzalari NL, Manthey BA, Vernon-Roberts B: The relationship between head-neck-shaft angle, calcar width, articular cartilage thickness and bone volume in arthrosis of the hip. *Br. J. Rheumatol.* 33, 432–436 (1994).

42 Gotfriedsen A, Riis BJ, Christiansen C, Rodbro P: Does a single local absorptiometric measurement indicate the overall skeletal status? Implications for osteoporosis and osteoarthritis of the hip. *Clin. Rheumatol.* 9, 193–203 (1990).

43 Bruckner P, Dreier R, Grässel S, Babarina AV: Common denominators of osteoarthritis and of endochondral bone formation: is osteoarthritis nothing but an inappropriate attempt at bone formation? *Z. Rheumatologie* 61, 263–265 (2002).

44 Burr DB, Radin EL: Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis? *Rheum. Dis. Clin. North Am.* 29, 675–685 (2003).

45 Dequeker J, Aerssens J, Luyten FP: Osteoarthritis and osteoporosis: clinical and research evidence of inverse relationship. *Aging Clin. Exp. Res.* 15, 426–439 (2003).

46 Clark JM: The structure of vascular channels in the subchondral plate. *J. Anat.* 171, 105–115 (1990).

47 Milz S, Putz R: Luckenbildung der subchondralen mineralisierungszone des tibia plateaus. *Osteologie* 3, 110–118 (1994).

48 Radin EL, Paul IL, Tolkoff MJ: Subchondral changes in patients with early degenerative joint disease. *Arthritis Rheum.* 13, 400–405 (1970).

49 Radin EL, Rose RM: Role of subchondral bone in the initiation and progression of cartilage damage. *Clin. Orthop.* 213, 34–40 (1986).

50 Aspden RM: Osteoarthritis: a problem of growth not decay? *Rheumatology (Oxford)* 47, 1452–1460 (2008).

▪ **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.**

51 Lin YY , Tanaka N, Ohkuma S *et al.*: Applying an excessive mechanical stress alters the effect of subchondral osteoblasts on chondrocytes in a co-culture system. *Eur. J. Oral Sci.* 118, 151–158 (2010).

▪ **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 illustrate that both an endogenous mechanism and a biomechanical stress contribute to OA pathology.**

52 Hannan MT, Anderson JJ, Zhang Y, Levy D, Felson DT: Bone mineral density and knee osteoarthritis in elderly men and women. *Arthritis Rheum.* 36, 1671–1680 (1993).

53 Dequeker J, Mohan R, Finkelman RD, Aerssens J, Baylink DJ: Generalized osteoarthritis associated with increased insulin-like growth factor types I and II and transforming growth factor β in cortical bone from the iliac crest. Possible mechanism of increased bone density and protection against osteoporosis. *Arthritis Rheum.* 36, 1702–1708 (1993).

54 Ferguson VL, Bushby AJ, Boyde A: Nanomechanical properties and mineral concentration in articular calcified cartilage and subchondral bone. *J. Anat.* 203, 191–202 (2003).

55 Ueno M, Shibata A, Yasui S, Yasuda K, Ohsaki K: A proposal on the hard tissue remineralization in osteoarthritis of the knee joint investigated by FT-IR spectrometry. *Cell Mol. Biol.* 49, 613–619 (2003).

56 Manacu CA, Martel-Pelletier J, Roy-Beaudry M *et al.*: Endothelin-1 in osteoarthritic chondrocytes triggers nitric oxide production and upregulates collagenase production. *Arthritis Res. Ther.* 7, R324–R332 (2005).

57 Fazzalari NL, Parkinson IH: Femoral trabecular bone of osteoarthritic and normal subjects in an age and sex matched group. *Osteoarthr. Cartil.* 6, 377–382 (1998).

58 Crane GJ, Fazzalari NL, Parkinson IH, Vernon-Roberts B: Age-related changes in femoral trabecular bone in arthrosis. *Acta Orthop. Scand.* 61, 421–426 (1990).

59 Dore D, Quinn S, Ding C, Winzenberg T, Cicuttini F, Jones G: Subchondral bone and cartilage damage: a prospective study in older adults. *Arthritis Rheum.* 62, 1967–1973 (2010).

60 Zysset PK, Sonny M, Hayes WC: Morphology-mechanical property relations in trabecular bone of the osteoarthritic proximal tibia. *J. Arthroplasty* 9, 203–216 (1994).

61 Mansell JP, Bailey AJ: Abnormal cancellous bone collagen metabolism in osteoarthritis. *J. Clin. Invest.* 101, 1596–1603 (1998).

62 Mansell JP, Tarlton JF, Bailey AJ: Biochemical evidence for altered subchondral bone collagen metabolism in osteoarthritis of the hip. *Br. J. Rheumatol.* 36, 16–19 (1997).

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).

64 Raynauld JP, Martel-Pelletier J, Berthiaume MJ *et al.*: Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. *Ann. Rheum. Dis.* 67, 683–688 (2008).

65 Simonet WS, Lacey DL, Dunstan CR *et al.*: Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell* 89, 309–319 (1997).

66 Shalitin S, Phillip M: Role of obesity and leptin in the pubertal process and pubertal growth – a review. *Int. J. Obes.* 27, 869–874 (2003).

67 Guymer E, Baranyay F, Wluka AE *et al.* A study of the prevalence and associations of subchondral bone marrow lesions in the knees of healthy, middle-aged women. *Osteoarthr. Cartil.* 15, 1437–1442 (2007).

68 Baranyay FJ, Wang Y, Wluka AE *et al.*: Association of bone marrow lesions with knee structures and risk factors for bone marrow lesions in the knees of clinically healthy, community-based adults. *Semin. Arthritis Rheum.* 37, 112–118 (2007).

69 Bennell KL, Creaby MW, Wrigley TV *et al.*: Bone marrow lesions are related to dynamic knee loading in medial knee osteoarthritis. *Ann. Rheum. Dis.* 69, 1151–1154 (2010).

70 Davies-Tuck ML, Wluka AE, Wang Y, English DR, Giles GG, Cicuttini F: The natural history of bone marrow lesions in community-based adults with no clinical knee osteoarthritis. *Ann. Rheum. Dis.* 68, 904–908 (2009).

71 Berry PA, Davies-Tuck ML, Wluka AE *et al.*: The natural history of bone marrow lesions in community-based middle-aged women without clinical knee osteoarthritis. *Semin. Arthritis Rheum.* 39, 213–217 (2009).

72 Bailey AJ, Sims TJ, Knott L: Phenotypic expression of osteoblast collagen in osteoarthritic bone: production of type I homotrimer. *Int. J. Biochem. Cell Biol.* 34, 176–182 (2002).

73 Truong LH, Kuliwaba JS, Tsangari H, Fazzalari NL: Differential gene expression of bone anabolic factors and trabecular bone architectural changes in the proximal femoral shaft of primary hip osteoarthritis patients. *Arthritis Res. Ther.* 8, R188 (2006).

74 Couchourel D, Aubry I, Delalandre A *et al.*: Altered mineralization of human osteoarthritic osteoblasts is due to abnormal collagen type 1 production. *Arthritis Rheum.* 60(5), 1438–1450 (2009).

75 Erlebacher A, Filvaroff EH, Gitelman SE, Derynck R: Toward a molecular understanding of skeletal development. *Cell* 80, 371–378 (1995).

76 DeLise AM, Fischer L, Tuan RS: Cellular interactions and signaling in cartilage development. *Osteoarthr. Cartil.* 8, 309–334 (2000).

77 Ornitz DM, Marie PJ: FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. *Genes Dev.* 16, 1446–1465 (2002).

78 Moon RT, Kohn AD, De Ferrari GV, Kaykas A: WNT and β-catenin signalling: diseases and therapies. *Nat. Rev. Genet.* 5, 691–701 (2004).

79 Willert K, Brown JD, Danenberg E *et al.*: Wnt proteins are lipid-modified and can act as stem cell growth factors. *Nature* 423, 448–452 (2003).

80 Zamurovic N, Cappellen D, Rohner D, Susa M: Coordinated activation of notch, Wnt, and transforming growth factor-β signaling pathways in bone morphogenic protein 2-induced osteogenesis. Notch target gene *Hey1* inhibits mineralization and *Runx2* transcriptional activity. *J. Biol. Chem.* 279, 37704–37715 (2004).

81 Maeda S, Hayashi M, Komiya S, Imamura T, Miyazono K: Endogenous TGF-β signaling suppresses maturation of osteoblastic mesenchymal cells. *EMBO J.* 23, 552–563 (2004).

82 Lee MH, Kim YJ, Kim HJ *et al.*: BMP-2-induced *Runx2* expression is mediated by Dlx5, and TGF-β 1 opposes the BMP-2-induced osteoblast differentiation by suppression of Dlx5 expression. *J. Biol. Chem.* 278, 34387–34394 (2003).

83 Laitinen M, Halttunen T, Jortikka L, Teronen O, Sorsa T, Lindholm TS: The role of transforming growth factor-β on retarded osteoblastic differentiation *in vitro*. *Life Sci.* 64, 847–858 (1999).

84 Rawadi G, Vayssiere B, Dunn F, Baron R, Roman-Roman S: BMP-2 controls alkaline phosphatase expression and osteoblast mineralization by a Wnt autocrine loop. *J. Bone Miner. Res.* 18, 1842–1853 (2003).

85 Lane NE, Nevitt MC, Lui LY, de Leon P, Corr M: Wnt signaling antagonists are potential prognostic biomarkers for the progression of radiographic hip osteoarthritis in elderly Caucasian women. *Arthritis Rheum.* 56, 3319–3325 (2007).

86 Olivares-Navarrete R, Hyzy S, Wieland M, Boyan BD, Schwartz Z: The roles of Wnt signaling modulators Dickkopf-1 (Dkk1) and Dickkopf-2 (Dkk2) and cell maturation state in osteogenesis on microstructured titanium surfaces. *Biomaterials* 31, 2015–2024 (2010).

87 van der Horst G, van der Werf SM, Farih-Sips H, van Bezooijen RL, Lowik CW, Karperien M: Downregulation of Wnt signaling by increased expression of Dickkopf-1 and -2 is a prerequisite for late-stage osteoblast differentiation of KS483 cells. *J. Bone Miner. Res.* 20, 1867–1877 (2005).

88 Smith AJ, Gidley J, Sandy JR *et al.*: Haplotypes of the low-density lipoprotein receptor-related protein 5 (*LRP5*) gene: are they a risk factor in osteoarthritis? *Osteoarthr. Cartil.* 13, 608–613 (2005).

89 Zhu M, Tang D, Wu Q *et al.*: Activation of β-catenin signaling in articular chondrocytes leads to osteoarthritis-like phenotype in adult β-catenin conditional activation mice. *J. Bone Miner. Res.* 24, 12–21 (2009).

90 Zhu M, Chen M, Zuscik M *et al.*: Inhibition of β-catenin signaling in articular chondrocytes results in articular cartilage destruction. *Arthritis Rheum.* 58, 2053–2064 (2008).

91 Yadav VK, Ryu JH, Suda N *et al.*: LRP5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell* 135, 825–837 (2008).

92 Warden SJ, Robling AG, Haney EM, Turner CH, Bliziotes MM: The emerging role of serotonin (5-hydroxytryptamine) in the skeleton and its mediation of the skeletal effects of low-density lipoprotein receptor-related protein 5 (LRP5). *Bone* 46, 4–12 (2010).

93 Lajeunesse M-P, Pelletier R: *The Role of Subchondral Bone in Osteoarthritis.* Sharma L, Berenbaum F (Eds). Mosby Elsevier, PA, USA, 15–32 (2007).

94 Aspden RM, Scheven BAA, Hutchison JD: Osteoarthritis as a systemic disorder including stromal cell differentiation and lipid metabolism. *Lancet* 357, 1118–1120 (2001).

95 Kesemenli CC, Memisoglu K, Muezzinoglu US: Bone marrow edema seen in MRI of osteoarthritic knees is a microfracture. *Med. Hypotheses* 72, 754–755 (2009).

96 Roemer FW, Guermazi A, Javaid MK *et al.*: Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. *Ann. Rheum. Dis.* 68, 1461–1465 (2009).

97 Ragab Y, Emad Y, Abou-Zeid A: Bone marrow edema syndromes of the hip: MRI features in different hip disorders. *Clin. Rheumatol.* 27, 475–482 (2008).

98 Murphy JM, Dixon K, Beck S, Fabian D: Reduced chondrogenic and adipogenic activity of mesenchymal stem cells from patients with advanced osteoarthritis. *Arthritis Rheum.* 46, 704–713 (2002).

99 Dumond H, Presle N, Terlain B *et al.*: Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum.* 48, 3118–3129 (2003).

100 Ku JH, Lee CK, Joo BS *et al.*: Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis. *Clin. Rheumatol.* 28, 1431–1435 (2009).

101 Miller GD, Nicklas BJ, Davis CC, Ambrosius WT, Loeser RF, Messier SP: Is serum leptin related to physical function and is it modifiable through weight loss and exercise in older adults with knee osteoarthritis? *Int. J. Obes. Relat. Metab. Disord.* 28, 1383–1390 (2004).

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

103 Massicotte F, Aubry I, Martel-Pelletier J, Pelletier JP, Fernandes J, Lajeunesse D: Abnormal insulin-like growth factor 1 signaling in human osteoarthritic subchondral bone osteoblasts. *Arthritis Res. Ther.* 8, R177 (2006).

104 Simopoulou T, Malizos KN, Iliopoulos D *et al.*: Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism. *Osteoarthr. Cartil.* 15, 872–883 (2007).

105 Elefteriou F, Takeda S, Ebihara K *et al.*: Serum leptin level is a regulator of bone mass. *Proc. Natl Acad. Sci. USA* 101, 3258–3263 (2004).

106 Ducy P, Amling M, Takeda S *et al.*: Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell* 100, 197–207 (2000).

107 Pallu S, Francin PJ, Guillaume C *et al.*: Obesity affects the chondrocyte responsiveness to leptin in patients with osteoarthritis. *Arthritis Res. Ther.* 12, R112 (2010).

108 Gevers G, Dequeker J: Collagen and non-collagenous protein content (osteocalcin, sialoprotein, proteoglycan) in the iliac crest bone and serum osteocalcin in women with and without hand osteoarthritis. *Coll. Relat. Res.* 7, 435–442 (1987).

109 Grynpas MD, Alpert B, Katz I, Lieberman I, Pritzker KPH: Subchondral bone in osteoarthritis. *Calcif. Tissue Int.* 49, 20–26 (1991).

110 Li B, Aspden RM: Mechanical and material properties of the subchondral bone plate from the femoral head of patients with osteoarthritis or osteoporosis. *Ann. Rheum. Dis.* 56, 247–254 (1997).

111 Lisignoli G, Toneguzzi S, Piacentini A *et al.*: CXCL12 (SDF-1) and CXCL13 (BCA-1) chemokines significantly induce proliferation and collagen type I expression in osteoblasts from osteoarthritis patients. *J. Cell Physiol.* 206, 78–85 (2006).

112 Hilal G, Martel-Pelletier J, Pelletier JP, Duval N, Lajeunesse D: Abnormal regulation of urokinase plasminogen activator by insulin-like growth factor 1 in human osteoarthritic subchondral osteoblasts. *Arthritis Rheum.* 42, 2112–2122 (1999).

113 Fazzalari NL, Forwood MR, Manthey BA, Smith K, Kolesik P: Three-dimensional confocal images of microdamage in cancellous bone. *Bone* 23, 373–378 (1998).

114 Fazzalari NL, Forwood MR, Smith K, Manthey BA, Herreen P: Assessment of cancellous bone quality in severe osteoarthrosis: bone mineral density, mechanics, and microdamage. *Bone* 22, 381–388 (1998).

115 Lane LB, Villacin A, Bullough PG: The vascularity and remodelling of subchondrial bone and calcified cartilage in adult human femoral and humeral heads. An age- and stress-related phenomenon. *J. Bone Joint Surg. Br.* 59, 272–278 (1977).

116 Radin EL, Paul IL, Lowy M: A comparison of the dynamic force transmitting properties of subchondral bone and articular cartilage. *J. Bone Joint Surg. Am.* 52, 444–456 (1970).

117 McKinley TO, Bay BK: Trabecular bone strain changes associated with subchondral stiffening of the proximal tibia. *J. Biomech.* 36, 155–163 (2003).

118 Brown AN, McKinley TO, Bay BK: Trabecular bone strain changes associated with subchondral bone defects of the tibial plateau. *J. Orthop. Trauma* 16, 638–643 (2002).

119 McKinley TO, Callendar PW, Bay BK: Trabecular bone strain changes associated with subchondral comminution of the distal tibia. *J. Orthop. Trauma* 16, 709–716 (2002).

120 Theoleyre S, Wittrant Y, Tat SK, Fortun Y, Redini F, Heymann D: The molecular triad OPG/RANK/RANKL: involvement in the orchestration of pathophysiological bone remodeling. *Cytokine Growth Factor Rev.* 15, 457–475 (2004).

121 Logar DB, Komadina R, Prezelj J, Ostanek B, Trost Z, Marc J: Expression of bone resorption genes in osteoarthritis and in osteoporosis. *J. Bone Miner. Metab.* 25, 219–225 (2007).

122 Fazzalari NL, Kuliwaba JS, Atkins GJ, Forwood MR, Findlay DM: The ratio of messenger RNA levels of receptor activator of nuclear factor κB ligand to osteoprotegerin correlates with bone remodeling indices in normal human cancellous bone but not in osteoarthritis. *J. Bone Miner. Res.* 16, 1015–1027 (2001).

123 Lavigne P, Shi Q, Lajeunesse D, Dehnade F, Fernandes JC: Metabolic activity of osteoblasts retrieved from osteoarthritic patients after stimulation with mediators involved in periprosthetic loosening. *Bone* 34, 478–486 (2004).

124 Kwan TS, Pelletier JP, Lajeunesse D, Fahmi H, Lavigne M, Martel-Pelletier J: The differential expression of osteoprotegerin (OPG) and receptor activator of nuclear factor κB ligand (RANKL) in human osteoarthritic subchondral bone osteoblasts is an indicator of the metabolic state of these disease cells. *Clin. Exp. Rheumatol.* 26, 295–304 (2008).

125 Tat SK, Pelletier JP, Lajeunesse D, Fahmi H, Duval N, Martel-Pelletier J: Differential modulation of RANKL isoforms by human osteoarthritic subchondral bone osteoblasts: influence of osteotropic factors. *Bone* 43, 284–291 (2008).

126 Fox KE, Colton LA, Erickson PF *et al.*: Regulation of *cyclin D1* and *Wnt10b* gene expression by cAMP-responsive element-binding protein during early adipogenesis involves differential promoter methylation. *J. Biol. Chem.* 283, 35096–35105 (2008).

127 Bennett CN, Ross SE, Longo KA *et al.*: Regulation of Wnt signaling during adipogenesis. *J. Biol. Chem.* 277, 30998–31004 (2002).

128 Li X, Liu P, Liu W *et al.*: DKK2 has a role in terminal osteoblast differentiation and mineralized matrix formation. *Nat. Genet.* 37, 945–952 (2005).

129 van Bezooijen RL, ten Dijke P, Papapoulos SE, Lowik CW: SOST/sclerostin, an osteocyte-derived negative regulator of bone formation. *Cytokine Growth Factor Rev.* 16, 319–327 (2005).

130 Kerkhof JM, Uitterlinden AG, Valdes AM *et al.*: Radiographic osteoarthritis at three joint sites and *FRZB*, *LRP5*, and *LRP6* polymorphisms in two population-based cohorts. *Osteoarthr. Cartil.* 16, 1141–1149 (2008).

131 Power J, Poole KE, van Bezooijen R *et al.*: Sclerostin and the regulation of bone formation: effects in hip osteoarthritis and femoral neck fracture. *J. Bone Miner. Res.* 25(8), 1867–1876 (2010).

132 Chan T, Couchourel D, Delalandre A, Lajeunesse D: Altered Wnt/β-catenin signaling in human osteoarthritic subchondral osteoblasts is due to altered Dickkopf-2 (DKK2) and prostaglandin E_2 (PGE_2) levels. *Osteoarthr. Cartil.* 17(Suppl. 1), S38 (2009).

133 Harrison MH, Schajowicz F, Trueta J: Osteoarthritis of the hip: a study of the nature and evolution of the disease. *J. Bone Joint Surg. Br.* 35B, 598–626 (1953).

134 Kadam UT, Jordan K, Croft PR: Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. *Ann. Rheum. Dis.* 63, 408–414 (2004).

135 Marks R, Allegrante JP: Comorbid disease profiles of adults with end-stage hip osteoarthritis. *Med. Sci. Monit.* 8, CR305–CR309 (2002).

136 Singh G, Miller JD, Lee FH, Pettitt D, Russell MW: Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. *Am. J. Manag. Care* 8, S383–S391 (2002).

137 Mori S, Harruff R, Burr DB: Microcracks in articular calcified cartilage of human femoral heads. *Arch Pathol. Lab. Med.* 117, 196–198 (1993).

138 Conaghan PG, Vanharanta H, Dieppe PA: Is progressive osteoarthritis an atheromatous vascular disease? *Ann. Rheum. Dis.* 64, 1539–1541 (2005).

139 Kougias P, Chai H, Lin PH, Yao Q, Lumsden AB, Chen C: Effects of adipocyte-derived cytokines on endothelial functions: implication of vascular disease. *J. Surg. Res.* 126, 121–129 (2005).

140 Pelletier JP, Martel-Pelletier J, Abramson SB: Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum.* 44, 1237–1247 (2001).

141 Lajeunesse D, Reboul P: Subchondral bone in osteoarthritis: a biologic link with articular cartilage leading to abnormal remodeling. *Curr. Opin. Rheumatol.* 15, 628–633 (2003).

142 Burr DB: The importance of subchondral bone in osteoarthrosis. *Curr. Opin. Rheumatol.* 10, 256–262 (1998).

143 Hulet C, Sabatier JP, Souquet D, Locker B, Marcelli C, Vielpeau C: Distribution of bone mineral density at the proximal tibia in knee osteoarthritis. *Calcif. Tissue Int.* 71, 315–322 (2002).

144 Lajeunesse D, Martel-Pelletier J, Fernandes JC, Laufer S, Pelletier JP: Treatment with licofelone prevents abnormal subchondral bone cell metabolism in experimental dog osteoarthritis. *Ann. Rheum. Dis.* 63, 78–83 (2004).

145 Bourguignon LY, Singleton PA, Zhu H, Zhou B: Hyaluronan promotes signaling interaction between CD44 and the transforming growth factor-β receptor I in metastatic breast tumor cells. *J. Biol. Chem.* 277, 39703–39712 (2002).

146 Westacott CI, Webb GR, Warnock MG, Sims JV, Elson CJ: Alteration of cartilage metabolism by cells from osteoarthritic bone. *Arthritis Rheum.* 40, 1282–1291 (1997).

147 Pelletier JP, Boileau C, Brunet J *et al.*: The inhibition of subchondral bone resorption in the early phase of experimental dog osteoarthritis by licofelone is associated with a reduction in the synthesis of MMP-13 and cathepsin K. *Bone* 34, 527–538 (2004).

148 Guévremont M, Martel-Pelletier J, Massicotte F *et al.*: Human adult chondrocytes express hepatocyte growth factor (HGF) isoforms but not HGF. Potential implication of osteoblasts for the HGF presence in cartilage. *J. Bone Miner. Res.* 18, 1073–1081 (2003).

149 Jiang J, Nicoll SB, Lu HH: Co-culture of osteoblasts and chondrocytes modulates cellular differentiation *in vitro*. *Biochem. Biophys. Res. Commun.* 338, 762–770 (2005).

150 Imhof H, Breitenseher M, Kainberger F, Rand T, Trattnig S: Importance of subchondral bone to articular cartilage in health and disease. *Top. Magn. Reson. Imaging* 10, 180–192 (1999).

151 Mital MA, Millington PF: Osseous pathway of nutrition to articular cartilage of the human femoral head. *Lancet* 1, 842 (1970) (Abstract).

152 Sokoloff L: Microcracks in the calcified layer of articular cartilage. *Arch Pathol. Lab. Med.* 117, 191–195 (1993).

153 Pan J, Zhou X, Li W, Novotny JE, Doty SB, Wang L: *In situ* measurement of transport between subchondral bone and articular cartilage. *J. Orthop. Res.* 27, 1347–1352 (2009).

▪ **First study to directly demonstrate that solute transport exists between the subchondral bone compartment and the overlying cartilage. Therefore, this study suggests that a putative factor(s) released by subchondral osteoblasts could reach the articular cartilage, thereby contributing to its degradation.**

154 Westacott CI, Webb GR, Elson CJ: Cells from osteoarthritic bone produce enzymes which degrade cartilage. *Trans. Orthop. Res. Soc.* 23, 919 (1998).