Published in final edited form as:

Bone. 2012 August ; 51(2): 197–203. doi:10.1016/j.bone.2012.01.008.

Role of Bone Architecture and Anatomy in Osteoarthritis

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Abstract

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

Introduction

In considering osteoarthritis (OA) as a “whole joint” disease, it is important to acknowledge the contribution of bone in addition to cartilage and synovium to the pathogenesis of the disease. Well-known radiographic features of OA, such as bony sclerosis and osteophyte formation, are helpful in diagnosis of OA but are thought to be results of the disease process rather than causative. Changes in bone certainly occur as a result of OA, but changes in bone architecture and biology may also contribute to the development of OA. Not only does bone in part determine the distribution of biomechanical forces across the joint, but changes in the bone itself may contribute to the evolution of OA in ways that are now beginning to be appreciated. This review will highlight the emerging evidence that bone plays a key role in the pathogenesis of OA, with special focus on the hip and knee joints. We will highlight the role of bone shape as a risk factor for OA in the hip and knee. This subject has also been the topic of prior reviews by our research group and others [1–6].

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Conflicts of Interest: The authors state no conflicts of interest.

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I. Does Bone Start the Ball Rolling in OA?

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

Perhaps the most persuasive evidence that bone contributes to the pathogenesis of OA comes from animal studies. In experimental models, surgical damage to subchondral bone leads to subsequent deterioration of the overlying articular cartilage, suggesting that bony changes may precede the cartilaginous changes of OA, at least in this model [11]. Muraoka and colleagues studied a strain of guinea pigs with spontaneously-occurring knee OA using a combination of histology, microfocal computed tomography (CT), and serum and urinary markers of bone turnover. They reported that animals with spontaneous knee OA demonstrate increased thickness of the subchondral bone plate, together with increased serum osteocalcin (a bone formation marker) and decreased urinary N-telopeptide (a bone degradation marker). Importantly, these changes were present before any histologic evidence of cartilage degradation [12]. In a mouse model of osteogenesis imperfecta, mice bearing a mutation of the bone-specific *Colla1* gene demonstrate the premature, aggressive development of OA at 2 months of age, as compared to wild-type mice, who demonstrated OA at 22 months of age [13]. Importantly, *Colla1*^{-/-} mice have genetically normal cartilage, so the degradation of articular cartilage in this animal model of OA occurs as a result of alterations in bone itself, as opposed to being the primary pathologic lesion.

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

The two main hypotheses of how bony changes may lead to cartilage deterioration are: (1) Changes in bone may alter the distribution of biomechanical forces across the joint cartilage, which in turn leads to cartilage degeneration [17], and (2) Altered bone metabolism results in the release of soluble biomediators causing the breakdown of overlying cartilage. In support of the first hypothesis, Buckland-Wright and colleagues used macroradiography, an

imaging technique using traditional X-ray beam equipment to increase the spatial resolution of the image compared to traditional plain films, to study in detail the early architectural changes of knee OA in humans [18]. They found that in advanced stages of knee OA, the trabeculae of subcortical bone remodel from the normal, cross-hatched pattern to a largely parallel pattern, which weakens the microarchitecture of the bone [16]. Animal models also support this idea. Wohl and colleagues studied the biomechanical properties of the knee joint in dogs following surgically-induced OA and found decreased yield stress and elasticity after transection of the anterior cruciate ligament [19]. In support of the second hypothesis, it is now known that channels connecting the subchondral bone to the overlying articular cartilage in the form of microcracks exist [20], and in vitro studies demonstrate a soluble mediator produced by osteoblasts may promote cartilage breakdown via diffusion through these channels [21, 22].

II. Changes in Subcortical Bone in Early OA: A Detailed Look

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

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

Another element of bone structure that is gaining increasing attention for its potential etiologic role in the development of knee OA is the bone marrow lesion (BML). These lesions were originally identified as areas of increased T2 or short-tau inversion recovery (STIR) signal on fat-suppressed MRI sequences. Felson and colleagues showed that the presence of large bone marrow lesions (over 1 cm² in cross-sectional area) was highly correlated with the presence of knee pain (odds ratio 5.8, 95% CI 1.04 to 111.1) [33] and with radiographic progression of knee OA over 15 months (odds ratio 6.5, 95% CI 3.0–14.0) [34]. Bone marrow lesions precede the development of radiographic OA detected by plain films, suggesting BMLs may represent early pathologic changes of OA [35]. Histologic examination of BMLs shows changes of osteonecrosis, fibrosis, and bone remodeling [36]

and ingrowth of fibrovascular tissue from the subchondral bone [37]. The pathologic significance of BMLs needs to be further defined, however, and it is important to note that BMLs are not specific to OA and may also be seen with osteonecrosis, rheumatoid arthritis, and trauma. As periosteum of bone is a richly innervated tissue, it is likely that part of the pain associated with OA comes from edema associated with BMLs, and part likely comes from structural changes in the bony cortex.

Advances in imaging and cellular techniques have allowed individual cell types of bone to be specifically examined for their potential roles in the evolution of OA.

Osteoblasts, the bone-forming cells, have been shown to display biological and morphological differences in subjects with and without OA. Shen and colleagues performed electron microscopy of the femoral heads of subjects with and without hip OA and found that osteoblasts in hip OA subjects showed evidence of increased active bone formation [38]. Osteoblasts are hypothesized to produce mediators of cartilage degradation in OA. Which factors are involved in the cross-talk between bone and cartilage has not yet been fully characterized, but preliminary reports have implicated transforming growth factor- β (TGF- β) [39], interleukin-6 (IL-6), IL-8 [40], insulin-like growth factors (IGFs), and matrix metalloproteinases (reviewed in [41], see also [40, 42, 43]). Presumably, bioactive mediators produced by osteoblasts diffuse to the articular cartilage via a series of channels connecting these two compartments [20]. Pan and colleagues demonstrated that diffusion between subchondral bone and articular cartilage is possible in the mouse knee using a small-molecule, fluorescein, in a proof-of-concept study [44].

Osteocytes are mechanosensory cells located within lacunae of the bone matrix. Confocal imaging shows osteocytes of subjects with OA are small and elongated compared to those of osteopenic or osteopetrotic bone [45]. Human studies using hip specimens obtained at joint replacement surgery demonstrate decreased expression of sclerostin, a WNT pathway antagonist, by bone osteocytes [46]. Decreased osteocyte production of sclerostin in turn results in increased WNT pathway signaling in osteoblasts and is thought to contribute to bony sclerosis seen in advanced hip OA [46].

III. Anatomic Bone Abnormalities Associated with Hip OA

Risk factors for OA of the hip include age, female sex, a history of hip injury, and exposure to sports and heavy mechanical loads [47–50]. Genes also play an important role as risk factors for hip OA, as it is estimated that this disease has a heritability of approximately 60% in women [51]. In addition to these risk factors, it is now known that the geometry of the hip joint itself is an important risk factor for OA, with subtle architectural changes predating the radiographic appearance of hip OA in up to 90% of cases [52, 53]. Individual differences in hip joint geometry alter the distribution of loading forces across the hip joint [54]. It is important to note that hip shapes predisposing to radiographic hip OA may be different from those predisposing to hip pain. Waarsing and colleagues, for example, showed that shapes of the femoral head that were associated with radiographic hip OA were distinct from those associated with symptomatic hip OA [55].

Acetabular dysplasia

Among the hip shapes that have been associated with OA of the hip is acetabular dysplasia, a term that encompasses a number of anatomic variants in the shape of the acetabular “cup” of the hip joint [52, 56–59]. Acetabular dysplasia was found to have a prevalence of 5% in the general U.S. population [60] and 3.4% in the general European population [61], both groups with a relatively high prevalence of hip OA. Acetabular retroversion, in which the acetabular cup is posteriorly oriented and fails to provide adequate coverage of the femoral

head anteriorly, is a subtype of acetabular dysplasia that has been linked to OA (OR 4.7, 95% CI 1.7 to 16.1 in [60]; see also [60, 62]). Using data from several epidemiologic studies, it can be estimated that between 25 and 40% of hip OA is attributable to acetabular dysplasia [52, 53, 63]. Importantly, a longitudinal study by Reijman and colleagues performed using the Rotterdam cohort demonstrated that acetabular dysplasia was present a mean of 6.6 years prior to the radiographic appearance of hip OA [57]. Similarly, Lane and colleagues found that acetabular dysplasia preceded the radiographic appearance of OA by a mean of 8.8 years in a cohort of postmenopausal women [56]. These latter studies suggest that the presence of acetabular dysplasia is a true risk factor for hip OA rather than a result of the disease process itself.

Femoroacetabular impingement

Femoroacetabular impingement (FAI) [64] describes a dynamic condition in which the femoral head and acetabulum impinge on one another during joint movement [65]. Two types of FAI have been described: (1) The “cam” variant in which an abnormally-shaped femoral head-neck junction impinges on the acetabular labrum during movement, and (2) the “pincer” variant in which an abnormally-shaped, “overcovering” acetabular labrum impinges on the femoral head. FAI often appears in young and middle-aged active adults [66, 67] and appears to be a risk factor for the development of hip OA later in life, though the precise attributable risk is not known [65]. Nicholls and colleagues performed a nested case-control study of 1003 women and found that the presence of the cam deformity on baseline radiograph predicted risk of total hip arthroplasty in the subsequent 18 years, though the effect was mild after adjustment for known confounders (OR ~1.06, $p < 0.001$) [68]. Wagner and colleagues studied cartilage samples from young adults undergoing orthopedic surgery for painful FAI and found that histologic changes similar to those seen in patients with advanced OA were present prior to radiographic changes [69]. This observation not only suggests that FAI is a true risk factor for OA but also that radiography is a relatively insensitive measure of early OA.

“Pistol grip” deformity

Nonspherical femoral head (“pistol grip” deformity) is a shape variant in which the femoral head-neck junction flattens along its superolateral aspect rather than having the usual concavity, producing a shape that resembles an old-fashioned pistol. This shape results in impingement of the femoral head against the acetabulum during movement and thus, the pistol grip deformity is one cause of FAI [70]. Doherty and colleagues compared 1007 cases with advanced hip OA recruited from orthopedic surgery lists to 1123 controls without radiographic hip OA and estimated an odds ratio of 6.95 (95% CI 4.6 to 10.4) for the association between pistol grip deformity and hip OA. Gosvig and colleagues reported a more modest association between pistol grip deformity and prevalent radiographic hip OA (OR 2.2, 95% CI 1.7 to 2.8, $p < 0.001$) [71]. In order to address the question of whether this deformity was present prior to the development of OA or occurred as the result of OA, Doherty and colleagues studied subjects with unilateral radiographic hip OA and assessed acetabular shape in the unaffected hip. This study found a significant correlation between acetabular shape of the unaffected hip with the presence of OA on the contralateral side, supporting the hypothesis that acetabular shape changes predate the appearance of hip OA [70].

Wide Femoral Neck

A wide femoral neck has been reported to be associated with hip OA in some [68, 72, 73] but not all studies. Nicholls and colleagues, for example, found in a European case-control study that women with increased femoral neck width at study year 2 were more likely to undergo total hip replacement surgery by study year 20 ($p < 0.0005$), though this variable was

not predictive of hip OA outcomes after adjustment for age and BMI [68]. Javaid and colleagues found in a cohort of 5245 post-menopausal Caucasian women that a wide femoral neck was associated with both prevalent and incident hip OA cases, suggesting that femoral neck widening may occur either as a result of or as a predisposing factor to hip OA [73]. Similarly, Waarsing and colleagues found the combination of a wide femoral neck and a small neck-shaft angle correlated with clinical OA of the hip [74], although femoral neck-shaft angle in and of itself has been only inconsistently associated with hip OA [70, 73, 75–77].

Global shape of the hip

In recent years, techniques for assessing global femoral shape rather than individual linear or angular measurements have been developed. One such technique is statistical shape modeling, in which a mathematical model of hip shape is developed using principal components analysis based on a series of spatial coordinates [78]. Gregory and colleagues performed a longitudinal study of 110 subjects from the Rotterdam cohort using statistical shape modeling of the proximal femur and found that not only did proximal femur shape change over time in subjects with OA, but also that even prior to the radiographic appearance of OA there were shape differences between OA cases and controls, again suggesting that shape changes precede as well as result from OA [79]. Lynch and colleagues similarly found differences in the shapes of the proximal femur in subjects who developed incident radiographic hip OA compared to controls that did not over an 8.3 year period [80]. Waarsing and colleagues recently extended these findings to a statistical shape model of the proximal femur and acetabulum that included information about the joint space [55], finding that these models described shape features associated with OA not captured by traditional radiographs.

IV. Anatomic Abnormalities Associated with Knee OA

It has long been appreciated that altered distribution of forces across the knee joint is a predisposing factor for OA, though research on how knee shapes are associated with the presence or progression of OA is still in its early phases. Obesity is a clear risk factor for OA, presumably because of an increase in biomechanical load [81]. It has also been appreciated for some time that malalignment of the knee is a predisposing factor for knee OA and that malalignment may interact with increased body mass index (BMI) to compound the risk of knee OA [82]. We will review some of the more recent findings linking subtle alterations in knee shape with the risk for OA.

Femur shape

Miura and colleagues examined subjects with multiple epiphyseal dysplasia, a disease causing abnormalities of the epiphysis of long bones in multiple anatomic locations associated with premature OA. This study found a shallow trochlear femoral groove was associated with the disease, suggesting it may also be a risk factor for OA [83]. Matsuda and colleagues analyzed MR images of osteoarthritic knees with either varus or valgus malalignment and found that the lateral femoral condyle was severely misshapen in knees with both valgus malalignment and OA compared to controls; a similar distortion of lateral condyle shape was not observed for osteoarthritis knees with varus malalignment [84]. Shepstone and colleagues studied human skeletons excavated from a burial site in England, making video images of an axial view of the distal femur, and found that a flattened shape to the intercondylar notch of the femur was associated with the presence of late-stage OA defined by eburnation [85].

Tibial shape

Nakamura and colleagues performed a simple shape analysis of the tibia, focusing on the directionality of the tibial spurs as determined by X-ray and its correlation with MRI findings of early knee OA [86]. They found that a downward-oriented medial tibial spine was associated with an increased risk of early cartilage degeneration of the knee. However, as this study was cross-sectional, no sequence could be inferred. Matsuda and colleagues examined anatomic features associated with varus malalignment on knee MRI and found that increased slope of the posterior tibia to be a risk factor [87]. Presumably, since varus malalignment also predisposes to medial compartment knee OA, this shape is also associated with knee OA, but this has not yet been shown.

Global shape of the tibiofemoral joint

The global shape of the tibiofemoral joint as a risk factor for OA of the knee has been explored using statistical shape modeling. Bredbenner and colleagues performed statistical shape modeling on magnetic resonance (MR) images from the Osteoarthritis Initiative (OAI) cohort and found that the shape of both the distal femur and the proximal tibia differed significantly between subjects with and without knee OA [88]. Specifically, the shape of the femoral condyles and the mid-intercondylar proximal tibia differed between subjects with and without knee OA, but the number of subjects was too few (n=12 per group) to fully characterize these differences. Haverkamp and colleagues performed statistical shape modeling of 609 woman in the Rotterdam cohort, including in their model the points from distal femur, the proximal tibia, patella, and medial femoral condyle outlined on a plain film of the knee [89]. They found that shapes corresponding to increased femoral and tibial width, increased height of the lateral tibial plateau, and increased extension of the knee joint were associated with an increased risk of knee OA [89].

Patellar shape

The patella, a sesamoid bone imbedded within the quadriceps tendon, is often overlooked when considering bony architecture of the knee in favor of the tibiofemoral joint. However, patellofemoral joint space disease has long been known to accompany OA of the knee, and recently, attention has turned to the possible contribution of the patella and the patellofemoral joint to the development of knee OA. Duncan and colleagues studied a population-based English cohort of subjects aged 50 and older with symptomatic knee pain and found patellofemoral OA to be slightly more common than tibiofemoral OA (cumulative 3-year incidence of 28.8% vs. 21.7%, respectively) [90]. This study suggested that radiographic OA changes appear in the patellofemoral joint prior to those in the tibiofemoral joint. Another group found that medial tilt of the patella as assessed by MRI was protective against knee pain in a community-based sample of adults aged 25 to 60 [91]. The shape of the trochlea, the groove of the femur in which the patella rests, also appears to be associated with patellofemoral joint OA, with more flattened lateral trochlea having an increased risk of OA (OR 2.6, 95% CI 1.9 to 2.7) [92].

V. Molecular Pathways Implicated for their Role in OA Pathogenesis: The WNT/ β -catenin and TGF- β /BMP Pathways

It is clear that gene expression in bone is altered in OA. Hopwood and colleagues performed a microarray study of bone samples obtained from subjects undergoing joint replacement for hip OA or cadaveric controls without OA and found that, among the many genes that were differentially expressed, components of two major biologic pathways emerged: the WNT (wingless integration) pathway and the transforming growth factor- β (TGF- β)/bone morphogenetic protein (BMP) pathway [93]. Interestingly, Sánchez-Sebaté and colleagues

performed a similar microarray study but instead used bone samples obtained from the iliac crest, a site considered to be remote from the areas involved in hip OA, and found that genes of these two pathways were also differentially expressed between subjects with and without OA, suggesting that the upregulation of these two pathways may occur more broadly in bone than previously thought [94].

The WNT pathway is of interest in discussing the link between bone shape and OA since WNT signaling is involved in both determining skeletal shape during early development [95] and in maintenance of bone and cartilage homeostasis in adult life [96]. Variant alleles of the WNT pathway antagonist FRZB have been linked to the development of hip and/or knee OA in some [97–102] but not all [103, 104] studies. The reasons for the conflicting reports are currently unclear but may involve differences in the precise definition of radiographic hip OA. Interestingly, Hiyama and colleagues found that the WNT and BMP pathways appear to have mutually opposing effects in cells cultured from the intervertebral disc, with activation of the WNT pathway promoting disc degeneration [105]. Pharmaceutical antagonists of the WNT/ β -catenin pathway are currently in development for the treatment of sclerotic lesions of multiple myeloma [106] and osteoporosis [107], but they have not yet been applied for treatment of OA.

The BMP pathway has also been highlighted recently for its potential role in OA. Among the genes in this pathway that have been linked to osteoarthritis are asporin (ASPN), BMP2, CILP, and growth and differentiation factor 5 (GDF) (reviewed in [108]). A BMP pathway antagonist is being applied to the treatment of osteolytic bony metastases of prostate cancer [109], and recombinant BMP7 is in development for treatment of OA [110, 111].

Potential utility of bisphosphonates to treat or prevent OA

The idea that bone changes may precede the degradation of cartilage in OA has led to the investigation of drugs that inhibit bone turnover and their potential role as disease-modifying agents in OA. Hayami and colleagues demonstrated that mice were protected from surgically-induced OA by the use of alendronate, presumably due to alendronate's role in inhibition of bone turnover [15]. Among subjects with knee OA progression, use of risedronate 15 mg daily protected against trabecular bone loss compared to risedronate 5 mg daily or placebo as assessed by fractal analysis [112]. Unfortunately, an international randomized, double-blind, placebo-controlled trial of subjects with medial knee OA defined both radiographically and symptomatically showed no effect of risedronate on slowing radiographic progression of the disease [113].

Conclusions

Increasing evidence suggests that bone and cartilage pathology are linked in osteoarthritis. Ideally, disease-modifying therapies for OA would target both bone and cartilage, as detrimental changes in these two compartments appear to be interconnected in the pathogenesis of OA.

Acknowledgments

This work was supported by the NIH Academic Rheumatology and Clinical Immunology Training Grant #AR007304 to J.C.B. and by 2K24-AR04884-06, R01 AR052000-01 A1, BAA-NHLBI-AR-10-06 grants and the Endowed Chair for Aging at U.C. Davis to N.E.L.

References

1. Karsdal MA, Leeming DJ, Dam EB, Henriksen K, Alexandersen P, Pastoureau P, Altman RD, Christiansen C. Should subchondral bone turnover be targeted when treating osteoarthritis? *Osteoarthritis Cartilage*. 2008; 16:638–46. [PubMed: 18362080]
2. Felson DT, Neogi T. Osteoarthritis: is it a disease of cartilage or of bone? *Arthritis Rheum*. 2004; 50:341–4. [PubMed: 14872473]
3. Lajeunesse D, Reboul P. Subchondral bone in osteoarthritis: a biologic link with articular cartilage leading to abnormal remodeling. *Curr Opin Rheumatol*. 2003; 15:628–33. [PubMed: 12960492]
4. Mansell JP, Collins C, Bailey AJ. Bone, not cartilage, should be the major focus in osteoarthritis. *Nat Clin Pract Rheumatol*. 2007; 3:306–7. [PubMed: 17538562]
5. Bullough PG. The role of joint architecture in the etiology of arthritis. *Osteoarthritis Cartilage*. 2004; 12 (Suppl A):S2–9. [PubMed: 14698635]
6. Baker-LePain JC, Lane NE. Relationship between joint shape and the development of osteoarthritis. *Curr Opin Rheumatol*. 2010; 22:538–43. [PubMed: 20644480]
7. Petersson IF, Boegard T, Svensson B, Heinegard D, Saxne T. Changes in cartilage and bone metabolism identified by serum markers in early osteoarthritis of the knee joint. *Br J Rheumatol*. 1998; 37:46–50. [PubMed: 9487250]
8. Hunter DJ, Hart D, Snieder H, Bettica P, Swaminathan R, Spector TD. Evidence of altered bone turnover, vitamin D and calcium regulation with knee osteoarthritis in female twins. *Rheumatology (Oxford)*. 2003; 42:1311–6. [PubMed: 12867590]
9. Hutton CW, Higgs ER, Jackson PC, Watt I, Dieppe PA. 99mTc HMDP bone scanning in generalised nodal osteoarthritis. II. The four hour bone scan image predicts radiographic change. *Ann Rheum Dis*. 1986; 45:622–6. [PubMed: 3740991]
10. 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*. 1993; 52:557–63. [PubMed: 8215615]
11. Mrosek EH, Lahm A, Erggelet C, Uhl M, Kurz H, Eissner B, Schagemann JC. Subchondral bone trauma causes cartilage matrix degeneration: an immunohistochemical analysis in a canine model. *Osteoarthritis Cartilage*. 2006; 14:171–8. [PubMed: 16242359]
12. Muraoka T, Hagino H, Okano T, Enokida M, Teshima R. Role of subchondral bone in osteoarthritis development: a comparative study of two strains of guinea pigs with and without spontaneously occurring osteoarthritis. *Arthritis Rheum*. 2007; 56:3366–74. [PubMed: 17907190]
13. Blair-Levy JM, Watts CE, Fiorentino NM, Dimitriadis EK, Marini JC, Lipsky PE. A type I collagen defect leads to rapidly progressive osteoarthritis in a mouse model. *Arthritis Rheum*. 2008; 58:1096–106. [PubMed: 18383364]
14. Nevitt MC, Lane NE, Scott JC, Hochberg MC, Pressman AR, Genant HK, Cummings SR. Radiographic osteoarthritis of the hip and bone mineral density. The Study of Osteoporotic Fractures Research Group. *Arthritis Rheum*. 1995; 38:907–16. [PubMed: 7612040]
15. Hayami T, Pickarski M, Wesolowski GA, McLane J, Bone A, Destefano J, Rodan GA, Duong le T. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. *Arthritis Rheum*. 2004; 50:1193–206. [PubMed: 15077302]
16. Buckland-Wright C. Subchondral bone changes in hand and knee osteoarthritis detected by radiography. *Osteoarthritis Cartilage*. 2004; 12 (Suppl A):S10–9. [PubMed: 14698636]
17. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. *Clin Orthop Relat Res*. 1986; 34–40. [PubMed: 3780104]
18. Davidson RA, Bowman S. Macroradiography using conventional radiographic X-ray equipment. *Br J Radiol*. 2002; 75:831–6. [PubMed: 12381692]
19. Wohl GR, Shymkiw RC, Matyas JR, Kloiber R, Zernicke RF. Periarticular cancellous bone changes following anterior cruciate ligament injury. *J Appl Physiol*. 2001; 91:336–42. [PubMed: 11408449]
20. Burr DB, Radin EL. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthritis? *Rheum Dis Clin North Am*. 2003; 29:675–85. [PubMed: 14603577]

21. Guevremont M, Martel-Pelletier J, Massicotte F, Tardif G, Pelletier JP, Ranger P, Lajeunesse D, Reboul P. Human adult chondrocytes express hepatocyte growth factor (HGF) isoforms but not HGF: potential implication of osteoblasts on the presence of HGF in cartilage. *J Bone Miner Res*. 2003; 18:1073–81. [PubMed: 12817761]
22. Westacott CI, Webb GR, Warnock MG, Sims JV, Elson CJ. Alteration of cartilage metabolism by cells from osteoarthritic bone. *Arthritis Rheum*. 1997; 40:1282–91. [PubMed: 9214429]
23. Bolbos RI, Zuo J, Banerjee S, Link TM, Ma CB, Li X, Majumdar S. Relationship between trabecular bone structure and articular cartilage morphology and relaxation times in early OA of the knee joint using parallel MRI at 3 T. *Osteoarthritis Cartilage*. 2008; 16:1150–9. [PubMed: 18387828]
24. Chiba K, Ito M, Osaki M, Uetani M, Shindo H. In vivo structural analysis of subchondral trabecular bone in osteoarthritis of the hip using multi-detector row CT. *Osteoarthritis Cartilage*. 19:180–5. [PubMed: 21087677]
25. Chiba K, Uetani M, Kido Y, Ito M, Okazaki N, Taguchi K, Shindo H. Osteoporotic changes of subchondral trabecular bone in osteoarthritis of the knee: a 3-T MRI study. *Osteoporos Int*.
26. Bailey AJ, Mansell JP, Sims TJ, Banse X. Biochemical and mechanical properties of subchondral bone in osteoarthritis. *Biorheology*. 2004; 41:349–58. [PubMed: 15299267]
27. Lo GH, Zhang Y, McLennan C, Niu J, Kiel DP, McLean RR, Aliabadi P, Felson DT, Hunter DJ. The ratio of medial to lateral tibial plateau bone mineral density and compartment-specific tibiofemoral osteoarthritis. *Osteoarthritis Cartilage*. 2006; 14:984–90. [PubMed: 16765066]
28. Lynch JA, Hawkes DJ, Buckland-Wright JC. Analysis of texture in macroradiographs of osteoarthritic knees using the fractal signature. *Phys Med Biol*. 1991; 36:709–22. [PubMed: 1871209]
29. Lynch JA, Hawkes DJ, Buckland-Wright JC. A robust and accurate method for calculating the fractal signature of texture in macroradiographs of osteoarthritic knees. *Med Inform (Lond)*. 1991; 16:241–51. [PubMed: 1921566]
30. Kraus VB, Feng S, Wang S, White S, Ainslie M, Brett A, Holmes A, Charles HC. Trabecular morphometry by fractal signature analysis is a novel marker of osteoarthritis progression. *Arthritis Rheum*. 2009; 60:3711–22. [PubMed: 19950282]
31. Messent EA, Buckland-Wright JC, Blake GM. Fractal analysis of trabecular bone in knee osteoarthritis (OA) is a more sensitive marker of disease status than bone mineral density (BMD). *Calcif Tissue Int*. 2005; 76:419–25. [PubMed: 15834503]
32. Messent EA, Ward RJ, Tonkin CJ, Buckland-Wright C. Tibial cancellous bone changes in patients with knee osteoarthritis. A short-term longitudinal study using Fractal Signature Analysis. *Osteoarthritis Cartilage*. 2005; 13:463–70. [PubMed: 15922180]
33. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, Kazis L, Gale DR. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med*. 2001; 134:541–9. [PubMed: 11281736]
34. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, Li W, Hill C, Gale D. Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med*. 2003; 139:330–6. [PubMed: 12965941]
35. Wluka AE, Hanna F, Davies-Tuck M, Wang Y, Bell RJ, Davis SR, Adams J, Cicuttini FM. 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*. 2009; 68:850–5. [PubMed: 18625617]
36. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. *Radiology*. 2000; 215:835–40. [PubMed: 10831707]
37. Saadat E, Jobke B, Chu B, Lu Y, Cheng J, Li X, Ries MD, Majumdar S, Link TM. Diagnostic performance of in vivo 3-T MRI for articular cartilage abnormalities in human osteoarthritic knees using histology as standard of reference. *Eur Radiol*. 2008; 18:2292–302. [PubMed: 18491096]
38. Shen Y, Zhang ZM, Jiang SD, Jiang LS, Dai LY. Postmenopausal women with osteoarthritis and osteoporosis show different ultrastructural characteristics of trabecular bone of the femoral head. *BMC Musculoskelet Disord*. 2009; 10:35. [PubMed: 19356253]

39. Mansell JP, Bailey AJ. Abnormal cancellous bone collagen metabolism in osteoarthritis. *J Clin Invest.* 1998; 101:1596–603. [PubMed: 9541489]
40. Sakao K, Takahashi KA, Arai Y, Saito M, Honjo K, Hiraoka N, Asada H, Shin-Ya M, Imanishi J, Mazda O, Kubo T. Osteoblasts derived from osteophytes produce interleukin-6, interleukin-8, and matrix metalloproteinase-13 in osteoarthritis. *J Bone Miner Metab.* 2009; 27:412–23. [PubMed: 19333684]
41. Lajeunesse D. The role of bone in the treatment of osteoarthritis. *Osteoarthritis Cartilage.* 2004; 12 (Suppl A):S34–8. [PubMed: 14698639]
42. 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, -1beta and oncostatin M pre-treated non-sclerotic osteoblasts. *Osteoarthritis Cartilage.* 2005; 13:979–87. [PubMed: 16243232]
43. Sanchez C, Deberg MA, Piccardi N, Msika P, Reginster JY, Henrotin YE. Subchondral bone osteoblasts induce phenotypic changes in human osteoarthritic chondrocytes. *Osteoarthritis Cartilage.* 2005; 13:988–97. [PubMed: 16168681]
44. 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.* 2009; 27:1347–52. [PubMed: 19360842]
45. van Hove RP, Nolte PA, Vatsa A, Semeins CM, Salmon PL, Smit TH, Klein-Nulend J. Osteocyte morphology in human tibiae of different bone pathologies with different bone mineral density--is there a role for mechanosensing? *Bone.* 2009; 45:321–9. [PubMed: 19398046]
46. Power J, Poole KE, van Bezooijen R, Doube M, Caballero-Alias AM, Lowik C, Papapoulos S, Reeve J, Loveridge N. Sclerostin and the regulation of bone formation: Effects in hip osteoarthritis and femoral neck fracture. *J Bone Miner Res.* 25:1867–76. [PubMed: 20200987]
47. Croft P, Coggon D, Cruddas M, Cooper C. Osteoarthritis of the hip: an occupational disease in farmers. *BMJ.* 1992; 304:1269–72. [PubMed: 1606427]
48. Wilson MG, Michet CJ Jr, Ilstrup DM, Melton LJ 3rd. Idiopathic symptomatic osteoarthritis of the hip and knee: a population-based incidence study. *Mayo Clin Proc.* 1990; 65:1214–21. [PubMed: 2402161]
49. Vingard E, Alfredsson L, Goldie I, Hogstedt C. Sports and osteoarthrosis of the hip. An epidemiologic study. *Am J Sports Med.* 1993; 21:195–200. [PubMed: 8465912]
50. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Ann Intern Med.* 2000; 133:321–8. [PubMed: 10979876]
51. MacGregor AJ, Antoniadou L, Matson M, Andrew T, Spector TD. The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. *Arthritis Rheum.* 2000; 43:2410–6. [PubMed: 11083262]
52. Harris WH. Etiology of osteoarthritis of the hip. *Clin Orthop Relat Res.* 1986:20–33. [PubMed: 3780093]
53. Murray RO. The aetiology of primary osteoarthritis of the hip. *Br J Radiol.* 1965; 38:810–24. [PubMed: 5842578]
54. Lenaerts G, Bartels W, Gelaude F, Mulier M, Spaepen A, Van der Perre G, Jonkers I. Subject-specific hip geometry and hip joint centre location affects calculated contact forces at the hip during gait. *J Biomech.* 2009; 42:1246–51. [PubMed: 19464012]
55. Waarsing JH, Rozendaal RM, Verhaar JA, Bierma-Zeinstra SM, Weinans H. A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip. *Osteoarthritis Cartilage.* 2010; 18:787–94. [PubMed: 20171297]
56. Lane NE, Lin P, Christiansen L, Gore LR, Williams EN, Hochberg MC, Nevitt MC. Association of mild acetabular dysplasia with an increased risk of incident hip osteoarthritis in elderly white women: the study of osteoporotic fractures. *Arthritis Rheum.* 2000; 43:400–4. [PubMed: 10693881]
57. Reijman M, Hazes JM, Pols HA, Koes BW, Bierma-Zeinstra SM. Acetabular dysplasia predicts incident osteoarthritis of the hip: the Rotterdam study. *Arthritis Rheum.* 2005; 52:787–93. [PubMed: 15751071]

58. Smith RW, Egger P, Coggon D, Cawley MI, Cooper C. Osteoarthritis of the hip joint and acetabular dysplasia in women. *Ann Rheum Dis.* 1995; 54:179–81. [PubMed: 7748014]
59. McWilliams DF, Doherty SA, Jenkins WD, Maciewicz RA, Muir KR, Zhang W, Doherty M. Mild acetabular dysplasia and risk of osteoarthritis of the hip: a case-control study. *Ann Rheum Dis.* 2010; 69:1774–8. [PubMed: 20472600]
60. Giori NJ, Trousdale RT. Acetabular retroversion is associated with osteoarthritis of the hip. *Clin Orthop Relat Res.* 2003;263–9. [PubMed: 14646725]
61. Jacobsen S, Sonne-Holm S, Soballe K, Gebuhr P, Lund B. Hip dysplasia and osteoarthritis: a survey of 4151 subjects from the Osteoarthritis Substudy of the Copenhagen City Heart Study. *Acta Orthop.* 2005; 76:149–58. [PubMed: 16097538]
62. Ezoe M, Naito M, Inoue T. The prevalence of acetabular retroversion among various disorders of the hip. *J Bone Joint Surg Am.* 2006; 88:372–9. [PubMed: 16452750]
63. Stulberg SD, Cordell LD, Harris WH, Ramsey PL, MacEwen GD. Unrecognised childhood hip disease: a major cause of idiopathic osteoarthritis of the hip. *Hip.* 1975; 3:212–30.
64. Ganz R, Parvizi J, Beck M, Leunig M, Notzli H, Siebenrock KA. Femoroacetabular impingement: a cause for osteoarthritis of the hip. *Clin Orthop Relat Res.* 2003;112–20. [PubMed: 14646708]
65. Macfarlane RJ, Haddad FS. The diagnosis and management of femoro-acetabular impingement. *Ann R Coll Surg Engl.* 92:363–7. [PubMed: 20626968]
66. Banerjee P, McLean CR. Femoroacetabular impingement: a review of diagnosis and management. *Curr Rev Musculoskelet Med.* 4:23–32. [PubMed: 21475562]
67. Maheshwari AV, Malik A, Dorr LD. Impingement of the native hip joint. *J Bone Joint Surg Am.* 2007; 89:2508–18. [PubMed: 17974896]
68. Nicholls AS, Kiran A, Pollard TC, Hart D, Arden CP, Spector T, Gill HS, Murray DW, Carr AJ, Arden NK. The association between hip morphology parameters and 19-year risk of end-stage osteoarthritis in the hip: A nested case-control study. *Arthritis Rheum.*
69. Wagner S, Hofstetter W, Chiquet M, Mainil-Varlet P, Stauffer E, Ganz R, Siebenrock KA. Early osteoarthritic changes of human femoral head cartilage subsequent to femoro-acetabular impingement. *Osteoarthritis Cartilage.* 2003; 11:508–18. [PubMed: 12814614]
70. Doherty M, Courtney P, Doherty S, Jenkins W, Maciewicz RA, Muir K, Zhang W. Nonspherical femoral head shape (pistol grip deformity), neck shaft angle, and risk of hip osteoarthritis: a case-control study. *Arthritis Rheum.* 2008; 58:3172–82. [PubMed: 18821698]
71. Gosvig KK, Jacobsen S, Sonne-Holm S, Palm H, Troelsen A. Prevalence of malformations of the hip joint and their relationship to sex, groin pain, and risk of osteoarthritis: a population-based survey. *J Bone Joint Surg Am.* 92:1162–9. [PubMed: 20439662]
72. Arokoski JP, Arokoski MH, Jurvelin JS, Helminen HJ, Niemitukia LH, Kroger H. Increased bone mineral content and bone size in the femoral neck of men with hip osteoarthritis. *Ann Rheum Dis.* 2002; 61:145–50. [PubMed: 11796401]
73. Javaid MK, Lane NE, Mackey DC, Lui LY, Arden NK, Beck TJ, Hochberg MC, Nevitt MC. Changes in proximal femoral mineral geometry precede the onset of radiographic hip osteoarthritis: The study of osteoporotic fractures. *Arthritis Rheum.* 2009; 60:2028–36. [PubMed: 19565486]
74. Waarsing JH, Rozendaal RM, Verhaar JA, Bierma-Zeinstra SM, Weinans H. A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip. *Osteoarthritis Cartilage.* 2010 Feb 18. [Epub ahead of print].
75. Mills HJ, Horne JG, Purdie GL. The relationship between proximal femoral anatomy and osteoarthritis of the hip. *Clin Orthop Relat Res.* 1993;205–8. [PubMed: 8458135]
76. 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.* 1994; 33:432–6. [PubMed: 8173846]
77. Reikeras O, Hoiseth A. Femoral neck angles in osteoarthritis of the hip. *Acta Orthop Scand.* 1982; 53:781–4. [PubMed: 7136589]
78. Cootes TF, Taylor CJ, Cooper DH, Graham J. Active shape models--their training and application. *Comput Vis Image Underst.* 1995; 61:38–59.

79. Gregory JS, Waarsing JH, Day J, Pols HA, Reijman M, Weinans H, Aspden RM. 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.* 2007; 56:3634–43. [PubMed: 17968890]
80. Lynch JA, Parimi N, Chaganti RK, Nevitt MC, Lane NE. The association of proximal femoral shape and incident radiographic hip OA in elderly women. *Osteoarthritis Cartilage.* 2009; 17:1313–8. [PubMed: 19427402]
81. Moio K, Chang A, Eckstein F, Chmiel JS, Wirth W, Almagor O, Prasad P, Cahue S, Kothari A, Sharma L. Varus-valgus alignment: reduced risk of subsequent cartilage loss in the less loaded compartment. *Arthritis Rheum.* 63:1002–9. [PubMed: 21225680]
82. Moyer RF, Birmingham TB, Chesworth BM, Kean CO, Giffin JR. Alignment, body mass and their interaction on dynamic knee joint load in patients with knee osteoarthritis. *Osteoarthritis Cartilage.* 18:888–93. [PubMed: 20417288]
83. Miura H, Noguchi Y, Mitsuyasu H, Nagamine R, Urabe K, Matsuda S, Iwamoto Y. Clinical features of multiple epiphyseal dysplasia expressed in the knee. *Clin Orthop Relat Res.* 2000:184–90. [PubMed: 11064990]
84. Matsuda S, Miura H, Nagamine R, Mawatari T, Tokunaga M, Nabeyama R, Iwamoto Y. Anatomical analysis of the femoral condyle in normal and osteoarthritic knees. *J Orthop Res.* 2004; 22:104–9. [PubMed: 14656667]
85. Shepstone L, Rogers J, Kirwan JR, Silverman BW. Shape of the intercondylar notch of the human femur: a comparison of osteoarthritic and non-osteoarthritic bones from a skeletal sample. *Ann Rheum Dis.* 2001; 60:968–73. [PubMed: 11557655]
86. Nakamura M, Sumen Y, Sakaridani K, Exham H, Ochi M. Relationship between the shape of tibial spurs on X-ray and meniscal changes on MRI in early osteoarthritis of the knee. *Magn Reson Imaging.* 2006; 24:1143–8. [PubMed: 17071336]
87. Matsuda S, Miura H, Nagamine R, Urabe K, Ikenoue T, Okazaki K, Iwamoto Y. Posterior tibial slope in the normal and varus knee. *Am J Knee Surg.* 1999; 12:165–8. [PubMed: 10496466]
88. Bredbenner TL, Eliason TD, Potter RS, Mason RL, Havill LM, Nicoletta DP. Statistical shape modeling describes variation in tibia and femur surface geometry between Control and Incidence groups from the osteoarthritis initiative database. *J Biomech.* 2010; 43:1780–6. [PubMed: 20227696]
89. Haverkamp DJ, Schiphof D, Bierma-Zeinstra SM, Weinans H, Waarsing JH. Variation in joint shape of osteoarthritic knees. *Arthritis Rheum.* 2011
90. Duncan R, Peat G, Thomas E, Hay EM, Croft P. Incidence, progression and sequence of development of radiographic knee osteoarthritis in a symptomatic population. *Ann Rheum Dis.*
91. Tanamas SK, Teichtahl AJ, Wluka AE, Wang Y, Davies-Tuck M, Urquhart DM, Jones G, Cicuttini FM. The associations between indices of patellofemoral geometry and knee pain and patella cartilage volume: a cross-sectional study. *BMC Musculoskelet Disord.* 11:87. [PubMed: 20459700]
92. Stefanik JJ, Roemer FW, Zumwalt AC, Zhu Y, Gross KD, Lynch JA, Frey-Law LA, Lewis CE, Guermazi A, Powers CM, Felson DT. Association between measures of trochlear morphology and structural features of patellofemoral joint osteoarthritis on MRI: The MOST Study. *J Orthop Res.*
93. Hopwood B, Tsykin A, Findlay DM, Fazzalari NL. Microarray gene expression profiling of osteoarthritic bone suggests altered bone remodelling, WNT and transforming growth factor-beta/bone morphogenic protein signalling. *Arthritis Res Ther.* 2007; 9:R100. [PubMed: 17900349]
94. Sanchez-Sabate E, Alvarez L, Gil-Garay E, Munuera L, Vilaboa N. Identification of differentially expressed genes in trabecular bone from the iliac crest of osteoarthritic patients. *Osteoarthritis Cartilage.* 2009; 17:1106–14. [PubMed: 19303468]
95. Witte F, Dokas J, Neuendorf F, Mundlos S, Stricker S. Comprehensive expression analysis of all Wnt genes and their major secreted antagonists during mouse limb development and cartilage differentiation. *Gene Expr Patterns.* 2009; 9:215–23. [PubMed: 19185060]
96. Corr M. Wnt-beta-catenin signaling in the pathogenesis of osteoarthritis. *Nat Clin Pract Rheumatol.* 2008; 4:550–6. [PubMed: 18820702]

97. Lane NE, Lian K, Nevitt MC, Zmuda JM, Lui L, Li J, Wang J, Fontecha M, Umbas N, Rosenbach M, de Leon P, Corr M. Frizzled-related protein variants are risk factors for hip osteoarthritis. *Arthritis Rheum.* 2006; 54:1246–54. [PubMed: 16572458]
98. Lories RJ, Boonen S, Peeters J, de Vlam K, Luyten FP. Evidence for a differential association of the Arg200Trp single-nucleotide polymorphism in FRZB with hip osteoarthritis and osteoporosis. *Rheumatology (Oxford).* 2006; 45:113–4. [PubMed: 16287928]
99. Loughlin J, Dowling B, Chapman K, Marcelline L, Mustafa Z, Southam L, Ferreira A, Ciesielski C, Carson DA, Corr M. Functional variants within the secreted frizzled-related protein 3 gene are associated with hip osteoarthritis in females. *Proc Natl Acad Sci U S A.* 2004; 101:9757–62. [PubMed: 15210948]
100. Min JL, Meulenbelt I, Riyazi N, Kloppenburg M, Houwing-Duistermaat JJ, Seymour AB, Pols HA, van Duijn CM, Slagboom PE. Association of the Frizzled-related protein gene with symptomatic osteoarthritis at multiple sites. *Arthritis Rheum.* 2005; 52:1077–80. [PubMed: 15818669]
101. Rodriguez-Lopez J, Pombo-Suarez M, Liz M, Gomez-Reino JJ, Gonzalez A. Further evidence of the role of frizzled-related protein gene polymorphisms in osteoarthritis. *Ann Rheum Dis.* 2007; 66:1052–5. [PubMed: 17237116]
102. Valdes AM, Loughlin J, Oene MV, Chapman K, Surdulescu GL, Doherty M, Spector TD. Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee. *Arthritis Rheum.* 2007; 56:137–46. [PubMed: 17195216]
103. Evangelou E, Chapman K, Meulenbelt I, Karassa FB, Loughlin J, Carr A, Doherty M, Doherty S, Gomez-Reino JJ, Gonzalez A, Halldorsson BV, Hauksson VB, Hofman A, Hart DJ, Ikegawa S, Ingvarsson T, Jiang Q, Jonsdottir I, Jonsson H, Kerkhof HJ, Kloppenburg M, Lane NE, Li J, Lories RJ, van Meurs JB, Nakki A, Nevitt MC, Rodriguez-Lopez J, Shi D, Slagboom PE, Stefansson K, Tsezou A, Wallis GA, Watson CM, Spector TD, Uitterlinden AG, Valdes AM, Ioannidis JP. Large-scale analysis of association between GDF5 and FRZB variants and osteoarthritis of the hip, knee, and hand. *Arthritis Rheum.* 2009; 60:1710–21. [PubMed: 19479880]
104. Kerkhof JM, Uitterlinden AG, Valdes AM, Hart DJ, Rivadeneira F, Jhamai M, Hofman A, Pols HA, Bierma-Zeinstra SM, Spector TD, van Meurs JB. Radiographic osteoarthritis at three joint sites and FRZB, LRP5, and LRP6 polymorphisms in two population-based cohorts. *Osteoarthritis Cartilage.* 2008; 16:1141–9. [PubMed: 18406176]
105. Hiyama A, Sakai D, Tanaka M, Arai F, Nakajima D, Abe K, Mochida J. The relationship between the Wnt/beta-catenin and TGF-beta/BMP signals in the intervertebral disc cell. *J Cell Physiol.* 2011; 226:1139–48. [PubMed: 20945354]
106. Gavriatopoulou M, Dimopoulos MA, Christoulas D, Migkou M, Iakovaki M, Gkatzamanidou M, Terpos E. Dickkopf-1: a suitable target for the management of myeloma bone disease. *Expert Opin Ther Targets.* 2009; 13:839–48. [PubMed: 19530987]
107. Li X, Ominsky MS, Warmington KS, Morony S, Gong J, Cao J, Gao Y, Shalhoub V, Tipton B, Haldankar R, Chen Q, Winters A, Boone T, Geng Z, Niu QT, Ke HZ, Kostenuik PJ, Simonet WS, Lacey DL, Paszty C. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res.* 2009; 24:578–88. [PubMed: 19049336]
108. Valdes AM, Spector TD. The clinical relevance of genetic susceptibility to osteoarthritis. *Best Pract Res Clin Rheumatol.* 2010; 24:3–14. [PubMed: 20129195]
109. Secondini C, Wetterwald A, Schwaninger R, Thalmann GN, Cecchini MG. The role of the BMP signaling antagonist noggin in the development of prostate cancer osteolytic bone metastasis. *PLoS One.* 2011; 6:e16078. [PubMed: 21249149]
110. Hayashi M, Muneta T, Takahashi T, Ju YJ, Tsuji K, Sekiya I. Intra-articular injections of bone morphogenetic protein-7 retard progression of existing cartilage degeneration. *J Orthop Res.* 2010; 28:1502–6. [PubMed: 20872588]
111. Hunter DJ, Pike MC, Jonas BL, Kissin E, Krop J, McAlindon T. Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis. *BMC Musculoskelet Disord.* 2010; 11:232. [PubMed: 20932341]

112. Buckland-Wright JC, Messent EA, Bingham CO 3rd, Ward RJ, Tonkin C. A 2 yr longitudinal radiographic study examining the effect of a bisphosphonate (risedronate) upon subchondral bone loss in osteoarthritic knee patients. *Rheumatology (Oxford)*. 2007; 46:257–64. [PubMed: 16837470]
113. Bingham CO 3rd, Buckland-Wright JC, Garnero P, Cohen SB, Dougados M, Adami S, Clauw DJ, Spector TD, Pelletier JP, Raynauld JP, Strand V, Simon LS, Meyer JM, Cline GA, Beary JF. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum*. 2006; 54:3494–507. [PubMed: 17075851]

Figure 1.
Illustrations of hip and knee shapes associated with osteoarthritis.