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Review
Should subchondral bone turnover be targeted when treating osteoarthritis?

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Summary

Objective: Osteoarthritis (OA) is the most common form of arthritic disease, and it is a major cause of disability and impaired quality of life in the elderly. OA is a complex disease of the entire joint, including bone and cartilage, thereby presenting alternative approaches for treatment. This review summarizes emerging observations from cell biology to preliminary clinical trials, describing interactions between the bone and cartilage components. We speculate whether a treatment for OA would be possible without targeting the bone compartment?

Methods: Peer-reviewed articles found using pre-defined search criteria and published in the PubMed database until June 2007 are summarized. In addition, abstracts from the OsteoArthritis Research Society International (OARSI) conferences in the time period 2000–2007 were included.

Results: Bone and cartilage health seem to be tightly associated. Ample evidence is found for bone changes during progression of OA, including, but not limited to, increased turnover in the subchondral bone, thinning of the trabecular structure, osteophytes, bone marrow lesions and sclerosis of the subchondral plate. In addition, a range of investigations has described secondary positive effects on cartilage health when bone resorption was suppressed, or deterioration of the cartilage when resorption is increased.

Conclusion: An optimal treatment for OA might include targeting both the bone and cartilage compartments. Hence, as several cell systems are to be targeted in a safe manner, limited options seem possible.

Key words: Osteoarthritis, Osteoclasts, Chondrocytes, Bone, Cartilage, Turnover, Sclerosis, Subchondral, Phenotype.

Introduction

Osteoarthritis (OA) is the most common form of arthritis[1]. A hallmark of the disease is progressive degeneration of articular cartilage and subsequent joint space narrowing (JSN).

Experimental and clinical observations suggest that the structural integrity of articular cartilage is dependent on normal subchondral bone turnover, intact chondrocyte function and ordinary biomechanical stresses[2,3]. An increasing line of evidence suggests that there are strong interrelationships between the subchondral bone and the articular cartilage. Therefore, in the face of normal biomechanical stresses, an ideal therapeutic agent might logically be directed at regulating the metabolic activity of both bone and cartilage.

In the majority of patients, the etiology of OA is not known. Among the known risk factors of OA are age, significant traumata, obesity, altered gait, altered biomechanics (e.g., varus or valgus deformity), and excessive loading[4–7]. Several lines of data indicate that OA could result from a metabolic component as evidenced by the finding that the decreased sex hormone levels in both animal models and women are associated with increased cartilage degradation, in addition to the well described increase in bone turnover[8–12]. Furthermore, the increased bone turnover leads to altered composition and biomechanical properties, which could exuberate the pathogenesis of OA[13–18].

Most of these studies were realized in humans and focused on late and end-stage disease, which reveals little about early deregulation of cartilage and bone turnover. However, a biochemical investigation of the circulating levels of macromolecules released from cartilage and bone in serum, during the early stage of OA in humans, suggests that pathological processes in cartilage and subchondral bone coincide in OA[19]. From this, there is an obvious interest in studying early bone and cartilage events in animal models and in clinical settings.

The use of biochemical markers has recently been proposed as a supplement to classical imaging techniques for improved diagnosis, and for monitoring of disease

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progression in studies of OA[20]. These provide dynamic measures, in contrast to imaging techniques that offer ''snap-shots'' of the current disease state. These novel techniques have aided in understanding the dynamics of bone and cartilage turnover, and could reveal possible metabolic processes in OA.

In this review we have focused on the role of the bone compartment in OA, and the apparent coupling between cartilage and bone turnover. We have taken into account experimental observations from pre-clinical and clinical studies, including interventions affecting both the bone and cartilage compartments.

Based on this evidence, the question becomes: ''Is it possible to inhibit cartilage health deterioration without targeting the joint as a whole organ, thereby involving multiple cell types, but most importantly both osteoclasts and chondrocytes?'' Having this difficult scene set for finding a possible disease modifying drug for OA, targeting several cell systems in a safe manner, only a limited number of options seem possible.

Methods

The PubMed database until September 2007 was searched, using the following search terms: cartilage, OA, subchondral, sclerosis, bone, biomechanical. In addition, articles were reviewed for other relevant references. Additional studies were found in a review of abstracts from the OsteoArthritis Research Society International (OARSI) conferences in the time period 2000–2006.

Results

THE ROLE OF SUBCHONDRAL BONE TURNOVER AND STRUCTURE IN OA

The relationship between bone and cartilage degradation in OA is complex, although an apparent co-existence between the two processes is present at a macroscopic observation scale[2].

Examinations of peri-articular bone in knees and hips of patients with OA have confirmed that the subchondral bone is abnormal in OA joints, with altered trabecular structure and sclerosis of the subchondral plate[21,22]. Bone scintigraphy has revealed localization of the nuclide to sites of increased subchondral bone turnover[23]. Cross-sectional studies have also established that women with advanced knee or hip OA have higher bone mineral densities (BMDs) near, or at the site of joint OA[24]. In fact, subchondral bone turnover has been shown to be as much as 20-fold increased compared to that of normal bone turnover[14].

Studies using anterior cruciate ligament transection (ACLT) in dogs as wells as meniscectomy (MNX) and ACLT in rat have provided instrumental information on the role of subchondral bone changes in OA[25–27]. During progression of OA the subchondral bone gradually becomes sclerotic, with bone formation in the periphery of the articular cartilage plate, both laterally and medially, resulting in osteophytes[2]. In addition, trabecular bone in the subchondral regions is thinned and elasticity is lost[25,27,28]. Findings, which have been speculated to be important for OA progression[25,27,28]. This combination of changes in the bone matrix are important features in the pathology of OA, although they are thought to be secondary effects caused by the loss of articular cartilage[2,3,13–17,26,29–33]. This is sought illustrated in Fig. 1.

Subchondral bone is separated from the articular cartilage only by a layer of calcified cartilage[34]. This allows for several possibilities of transmitting signals from one compartment to the other. Among these are increased vascularization, and the development of microcracks occurring in the bone matrix, both phenomena which have been strongly implicated in initiation of bone remodeling, as well as increased degradation of the calcified cartilage[34,35]. In alignment, in race horses, micro-crack propagation in the calcified cartilage and subchondral bones, was speculated to be involved in the initiation of articular cartilage breakdown, and thereby initiation and progression of OA[36–38].

Subchondral bone turnover may logically depend on osteoclastic activities. Osteoclasts have been shown to play important roles in the degradation of cartilage in rheumatoid arthritis (RA)[39–42], whereas the role of osteoclasts in the pathogenesis of OA still needs more attention. Support for the important role of osteoclast function and bone turnover in the pathogenesis of OA, recently came from an animal model of OA, where extensive inhibition of bone resorption resulted in a 50% decrease in cartilage pathology score, using the golden standard Mankin score[3,26]. In addition, a bone densitometric evaluation in the meniscectomized guinea pig model of OA revealed typical variations of bone metabolism in the initiation of the OA pathology with an early bone loss at the subchondral level followed

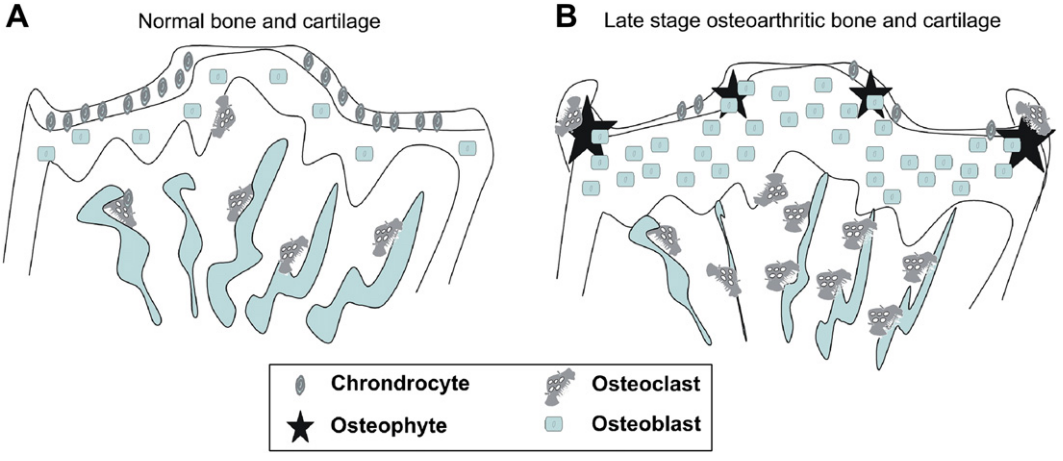

Fig. 1. Schematic illustration of the alterations in the subchondral area. Right panel A: normal tibial plateau. Left panel B: osteoarthritic tibial plateau, showing loss of cartilage, increased bone turnover, sclerosis of the subchondral plate, thinning of the trabeculae, and osteophytes.

by an increased bone density[43]. This finding corroborates previous extensive findings of altered subchondral turnover in the pathogenesis of OA[13–17,29,44]. In alignment, accelerated bone turnover, in both traumatic and estrogen deficiency models [ovariectomy (OVX)], in which increased bone resorption alone results in increased articular damage[31] has been shown to augment articular cartilage erosion[9–12,30]. Finally, evidence from the Dunkin–Hartley guinea pig model indicates that subchondral changes precede the changes in the cartilage[45,46], thereby further supporting a role for bone remodeling in the development of OA.

Taken together, bone turnover and osteoclast functions are important elements in the pathogenesis of OA, in which both osteoclastic bone resorption and signals coming from osteoclasts may play important roles[47] in the different sclerotic and osteoporotic and sub-compartments of bone.

ALTERATIONS IN THE OSTEOBLAST, OSTEOCLAST AND BONE PHENOTYPES IN THE PATHOGENESIS OF OA

Whereas on a macroscopic observational scale there is an almost obvious coupling of bone and cartilage processed[13–17,29], the cellular and molecular mechanisms remain to be further investigated and identified.

Recently, TGF-β signaling which is known to play several important roles in bone and cartilage, was suggested to be involved in the coupling between bone and cartilage turnover[3,13,29]. Furthermore, interleukin (IL)-6 has also been implicated in the cross-talk between bone and cartilage, and studies have shown that IL-6 in combination with other cytokines can switch osteoblasts from a normal phenotype to a sclerotic phenotype[48], as well as altering expression of different chemokines, such as regulated on activation, normal T cell expressed and secreted (RANTES) and monocyte chemoattractant protein (MCP-1)[49]. In addition, male IL-6 deficient mice shown increased age-related OA[50], further indicating that IL-6 plays a role in OA. However, the present understanding remains on an observational level, in which an increasing range of experimental evidence is emerging.

With respect to changes at the molecular level, osteoarthritic bone matrix in the subchondral plate has been shown to have alterations in collagen turnover and structure, cytokine expression, as well as mineralization[17,51]. In this, OA results in increased bone formation, assessed by Alkaline Phosphatase and levels of C-terminal pro-peptide of type I collagen (PICP)[29] and associated hypomineralized bone, indicating compromised structural integrity[29]. The compromised bone integrity was corroborated by Bailey *et al.* who demonstrated that the composition of collagen trimers was altered towards homotrimers of the alpha1 chain, which are associated with lower tensile strength[52]. In addition, the hydroxylation of the lysines was increased leading to increased cross-linking, further contorting the collagen structure[52], and not surprisingly the bone matrix was demonstrated to have impaired mechanical strength[53], despite the increased density.

With regards to the cellular phenotype, only little information is available. Experiments performed using isolated osteoblasts form OA patients have shown increased proteoglycan degradation in cartilage, in contrast to healthy controls[54]. This has been suggested to be a result of increased matrix metalloproteinase (MMP)-2 expression of these bones[29]. This may indicate a role for altered osteoblast phenotypes during disease development, resulting in the above-described alterations in matrix function and composition. In addition, a group has shown that osteoblasts from the sclerotic regions of bone isolated from OA patients could be involved in induction of chondrocyte hypertrophy[55]. Furthermore, the same group also demonstrated that the sclerotic osteoblasts were capable of switching the profile of chondrocytes towards cartilage degradation, as illustrated by a reduction in aggrecan production, but an upregulation of MMP production[48]. Finally, a study showed that the bone remodeling rates in healthy individuals correlate to receptor activator of nuclear factor-kappaB ligand (RANKL) expression levels, whereas in OA patients this correlation is no longer existing[56]. As osteoblasts are a major source of RANKL[57,58], this further supports the view that changes in osteoblasts are involved in OA pathology and progression.

With respect to the phenotype of osteoclasts in the pathogenesis of OA, only sparse information is available. Recently, a study showed that a powerful anti-resorptive, the bisphosphonate alendronate, suppressed cartilage degradation and formation of osteophytes in a rat model, an effect most likely mediated *via* a reduction in osteoclast numbers and activity[3]. In this, alendronate treatment reduced the release of TGF-β[3], a cytokine which is present at abnormally high levels in OA[59], and speculated to be important in the coupling of cartilage and bone turnover[13]. The exact role and phenotype of osteoclasts in the development of OA needs attention. It is of major interest to investigate whether the osteoclasts involved in the development of OA, indeed are authentic osteoclasts or chondroclasts, i.e., whether osteoclasts localized on calcified cartilage in the subchondral bone are different from those on normal bone matrix, as these may not be identical[60,61]. Drawing a parallel to rheumatoid arthritis (RA), which is characterized by excessive osteoclast function, and in models of RA, anti-osteoclastic treatments, such anti-RANKL approaches, reduce the extent of the disease[42,62].

Taken together, it appears that osteoclastic bone resorption, bone formation by the osteoblasts, and signals coming from both osteoclasts and osteoblasts may play important roles in the mal-metabolism of the subchondral bone during pathogenesis of OA[13,47].

A POSSIBLE BIOMECHANICAL COUPLING OF BONE AND CARTILAGE

The possible coupling between bone and cartilage has also been investigated using novel magnetic resonance imaging (MRI) techniques. MRI has been validated for analysis of trabecular structure by comparison to μCT, in which in particular 3 T imaging has demonstrated a high correlation between MRI and μCT based measures[63,64]. Blumenkrantz *et al.* undertook MRI analyses, which were applied to compare longitudinal changes in bone density and quality, assessed by apparent trabecular structure, which were correlated to changes in cartilage volume and quality[63]. They concluded that there was a positive correlation between cartilage loss and localized bone changes closest to the joint line, specifically; the cartilage loss and the decrease in apparent trabecular count were correlated in both the medial ($r = 0.36$, $P < 0.05$) and the lateral ($r = 0.41$, $P < 0.05$) tibial chondyles. Furthermore, negative correlations were observed with the bone changes farthest from the joint line (e.g., the medial tibial cartilage volume was negatively correlated with the apparent bone volume fraction of the tibia, $r = -0.53$, $P < 0.05$). They hypothesized that cartilage degeneration coincides locally with subchondral bone sclerosis, which then causes subchondral

bone osteopenia due to decreased load transmission[64]. Reactive bone formation may then occur farther away from the cartilage abnormality in order to compensate for the localized bone loss.

Applying the same methodology, Lindsey and colleagues found that cartilage loss in the medial compartment directly correlated to bone formation in the medial chondyle, and to bone resorption in the lateral compartment. Specifically, the medial tibial cartilage volume was positively correlated to lateral apparent trabecular count ($r = 0.33$, $P = 0.005$)[65]. This relationship is illustrated in Fig. 2. Furthermore, by analyzing differences between lateral/medial measurements, they hypothesized that these cross-compartmental relationships are consistent with biomechanical changes in load distribution caused by varus mal-alignment. Using conventional radiographs Messent *et al.* presented similar findings. From knee macro-radiographs of 40 patients, they demonstrated that JSN was associated with a decrease of the subchondral trabecular number[66]. They hypothesized that thickening of the cortical plate; occurring before JSN, caused a load redistribution that reduced the subarticular stress leading to osteoporosis (OP).

These studies support a biomechanical coupling relationship between cartilage and bone in OA, although they do not provide clear indications of the causal relationship. The observation that cortical thickening occurs before JSN does not necessarily imply that bone changes are prior to cartilage changes, since JSN occurs relatively late in the evolution of OA. However, these studies do provide additional support for the close spatial and temporal relationship between bone and cartilage.

METABOLIC OA

Metabolic OA, showing a systemic increased turnover of cartilage, is found in postmenopausal women in whom OA is more pronounced, than in the pre-menopausal population[8,67–70]. An epidemiological study supports the concept that women, in addition to age, are at a higher risk than men[71]. This indirectly supports the hypothesis that sex hormones are related to the incidence of OA. In addition, experimental studies in monkeys[30,31] and rats[72] have shown that estrogen depletion results in increased bone turnover, and accelerated cartilage breakdown. These observations are somewhat complicated by the fact that chondrocytes have been shown to express estrogen receptors[73–75], and respond to estrogen intervention[76], however, it is not believed that this accounts for the entire detrimental effect of estrogen loss on cartilage health[77].

A relationship between OP and OA has been demonstrated in female rabbits[9]. Here induction of OA was performed by anterior cruciate section and partial medial MNX in 12 animals, and OP by OVX in six of these prior to OA induction. OP increased the severity of OA compared to animals without OP and an inverse correlation was observed between BMD at the lumbar spine and cartilage damage defined as increased Mankin scoring. These data indicate that a higher bone turnover exuberates the OA characteristics. In alignment, development of OA was followed in mice having destabilization of the medial meniscus (DMM). Half of these animals were orchiectomized (ORX, male mice) or OVX (female mice)[10]. OA severity was markedly higher in DMM male mice than DMM female mice. However, OVX female mice developed more severe OA compared to controls, whereas ORX male mice develop significant less severe OA than control mice.

Taken together, this compilation of data indicates that increases in bone turnover, due to sex hormone deficiency, play a critical role in the progression of OA in both mouse models and humans, even though potential direct hormone effects on the chondrocytes cannot be ruled out.

BIOCHEMICAL MARKERS OF BONE AND CARTILAGE TURNOVER

Bone and cartilage degradation can be measured by biochemical markers, such as bone resorption by cross-linked C-terminal type I collagen fragments (CTX-I), reflecting type I collagen[78] and cartilage degradation by CTX-II, reflecting type II collagen[79]. These markers have been used extensively for the evaluation of these parameters in basic, experimental and clinical studies[20].

In a subgroup of the OFELY (Os des Femmes de Lyon) study, 435 healthy untreated younger postmenopausal women were followed for 5 years to predict the risk of fracture[80]. Women in the highest quartile of baseline bone marker level were found to have a relative risk of fracture of 2.1, emphasizing the relevance and importance of the biochemical markers of bone turnover. With respect to cartilage degradation and the use of biochemical markers, a cross-sectional and longitudinal study of 1235 men and women from Rotterdam examined the association between CTX-II and the radiographic prevalence and progression of OA in the knee and hip[81]. Subjects with CTX-II levels in the highest quartile at baseline had a 4.2-fold increased risk of

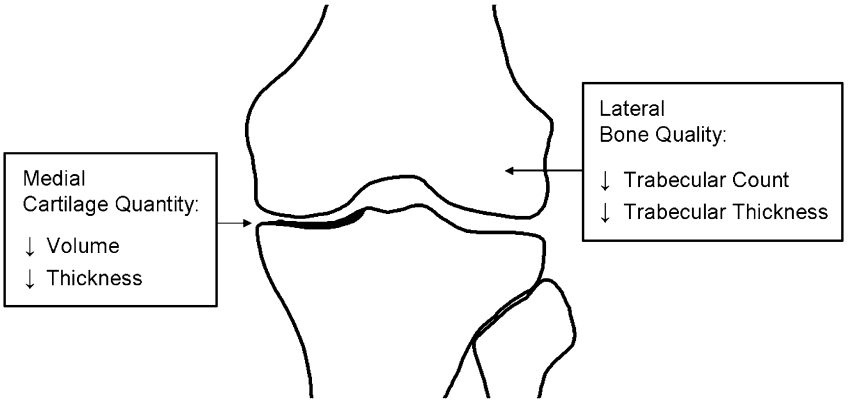

Fig. 2. Biomechanical coupling: medial cartilage loss is correlated to loss of lateral trabecular structure[65] revealing a potential biomechanical coupling between bone and cartilage. Illustration inspired by Lindsey *et al.*[65]

having radiographic OA of the knee and hip, as compared to subjects in the lowest quartile. The risk of disease progression was 6.0-fold increased in the knee and 8.4-fold increased in the hip of the same patients determined at follow-up. Thus, the highest risk of OA and progression was found in patients with the highest baseline levels of CTX-II. A similar finding, namely that those individual with the highest CTX-II levels had the highest odds ratio for having OA was validated in the genetics, arthrosis and progression (GARP) study of sibling pairs, in which symptomatic OA and the levels of a number of biochemical markers were assessed[82]. Results showed a direct correlation between CTX-II and radiographic signs of OA in signals joints ($P < 0.001$)[48], and that those with the highest CTX-II levels had a 7.7 increased odd ratio for having OA.

Taken together, biochemical markers of bone and cartilage destruction may be valuable for the interpretations of the biological processes and for determining the sequence of bone and cartilage changes, leading to a better understanding of disease progression in OA.

ANTI-RESORPTIVE STRATEGIES IN OA: NON-CLINICAL STUDIES AND ANTI-RESORPTIVE TREATMENTS

An alternative approach to investigate the coupling between bone and cartilage turnover and deterioration in the pathogenesis in OA is through analysis of the response to various treatments in both pre-clinical and clinical studies. A 3-year study examined the effect of anti-resorptive estrogen replacement therapy (ERT) for the prevention of OA in 180 female cynomolgus monkeys[30,31]. Ovariectomized adult monkeys were divided into groups receiving ERT or receiving no treatment. Significantly fewer cartilage lesions of OA were seen in the ERT group compared to the control group, as evaluated by quantitative histology. The authors suggested that high bone turnover co-equals high risk for cartilage degradation and that exogenous estrogens may confer protection against the development of OA. As mentioned previously, Duong and colleagues investigated the effects of bone turnover and development of OA by the use of intravenous (i.v.) bisphosphonate treatment in a traumatic model of OA, the ACLT model[3,26]. Bisphosphonate treatment resulted in a 50% decrease in disease severity scores OA, further emphasizing the importance and coupling between bone and cartilage health.

Additional support for the role of the subchondral bone was found in studies examining the effect of calcitonin in ACLT dogs. Calcitonin significantly affected trabecular structure and prevented subchondral bone resorption and trabecular thinning, which was speculated to a major factor in the reduced cartilage degradation[83–85]. The mode of action of calcitonin may be different compared to that of other anti-resorptives, as calcitonin was demonstrated to have both direct and indirect actions on articular cartilage[83–95]. In golden standard traumatic and non-traumatic animal models of OA, i.e., the dog ACLT model, calcitonin has been demonstrated to have positive effects on articular cartilage surface erosion and bone structure as well as increased proteoglycan content of the articular cartilage[84,86,95,96].

Taken together, this increasing line of evidence, points toward the fact that that some anti-resorptive treatments, such as bisphosphonates, calcitonin, estrogen or selective estrogen-receptor modulators (SERMs) have positive effects on both cartilage and bone degradation, possibly due to a tight coupling between these compartments. Some of these possible intervention options may, in addition to the effects on osteoclasts and bone turnover, provide additional benefits by targeting chondrocytes directly.

ANTI-RESORPTIVE STRATEGIES IN OA: CLINICAL STUDIES

A number of studies have investigated the coupling between bone and cartilage degradation. We have previously demonstrated the therapeutical benefit of a SERM, levormeloxifene, in 301 postmenopausal women from a phase II trial, for the prevention of both bone loss and cartilage degradation by restoring levels to that of the pre-menopausal level during a 12-month period[12]. Both cartilage and bone degradation assessed by CTX-II and CTX-I were decreased by approximately 50% in the treatment groups compared to baseline. After treatment cessation CTX-II reversed back to baseline values, indicating a short-term effect of the SERM on the cartilage as compared to that on bone. Similarly, another group found that cartilage degradation in 384 postmenopausal women was significantly lower in women using HRT compared to women not receiving hormone replacement therapy (HRT)[8]. Additionally, groups receiving between 4 and 10 years of HRT had significant lower CTX-II than those receiving less than 4 years of treatment. It was observed that degradation was significantly higher in postmenopausal women compared to an age-matched group of pre-menopausal women.

Effects of calcitonin on both bone and cartilage have raised interest in using it as a therapy for OA. Calcitonin was demonstrated to have chondroprotective effects in two different clinical trials[93,96]. In these, calcitonin showed both effects on pain scores, and biochemical markers of cartilage degradation. However, additional clinical studies are needed to further investigate and validate these findings.

In some instances administration of anti-resorptive drugs to patients cause a decrease in both cartilage degradation and bone resorption[8,12,97]. In therapy of Paget's disease, one dose intravenously administered zoledronate resulted in a reduction of CTX-II and CTX-I at 1 month[97]. At baseline, CTX-II levels were not elevated compared to a group of age-matched healthy controls. This was in contrast to a ninefold increase in CTX-I compared to controls. Five days after a single 4-mg dose of zoledronate, CTX-II decreased by a median of 25% and then increased to pre-treatment levels 10 days after injection. CTX-I decreased a maximum of 51% at day 10 and levels remained suppressed during the 2 months of the study indicating that zoledronate has a long-term effect on bone resorption as well as a short-term effect on cartilage. This is in contrast of the effect of oral bisphosphonates in which a long-term effect on both and cartilage is observed[98,99]. Thus, different anti-resorptive agents, and even routes of administration, appear to have different effects on cartilage.

Discussion

The potential coupling and uncoupling of bone and cartilage turnover are illustrated in Fig. 3. Under physiological conditions, bone and cartilage turnover are coupled. Increased bone resorption can exist together with increased cartilage degradation, but within the normal biological variation. Under pathological conditions of extremely high turnover, such as bone metastasis, bone resorption is highly elevated, although cartilage degradation is only minutely affected, thus these processes are uncoupled.

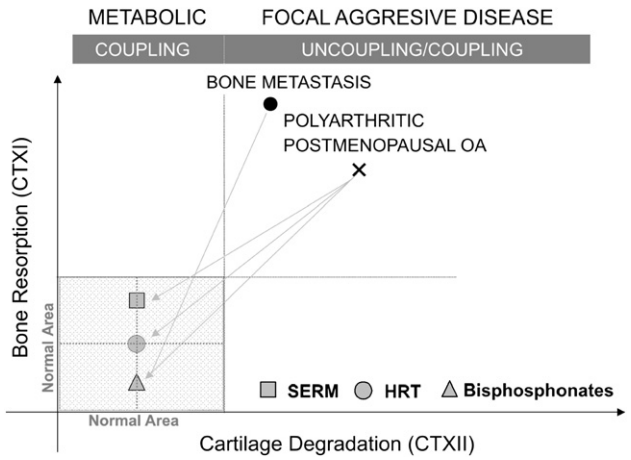

Fig. 3. Schematic figure showing the coupling/uncoupling relationship between cartilage and bone. Under normal physiological conditions, bone and cartilage turnover are coupled (lower left quadrant). In bone metastasis where pathologically increased bone turnover is observed, cartilage turnover is only minimally affected. In contrast, in postmenopausal OA both bone and cartilage are increased, probably due to increased metabolic activity in subchondral bone. Some anti-resorptive agents, such as estrogens, SERMs, bisphosphonates, and calcitonin inhibit increased bone turnover and also the increased cartilage turnover, in part through direct interaction of attenuating subchondral bone turnover, and possibly by direct action receptors activated action on chondrocytes. Additional data on anti-RANKL and strontium ranelate are needed in order to correctly incorporate them into this model.

By treatment with a bisphosphonate the levels of bone resorption can be restored to normal levels, whereas cartilage degradation is only vaguely affected[97].

In contrast, during postmenopausal increased high turnover, both bone resorption and bone formation can be restored back to normal levels. HRT will restore both levels to pre-menopausal levels, whereas a SERM will have lower efficacy on bone. In alignment, treatment with bisphosphonates will suppress bone resorption to lower levels than cartilage degradation.

Presence and activation of osteoclasts seem to be involved in the pathogenesis of OA and other cartilage degenerative diseases[41,42]. Increased expression of osteoclast differentiation factors RANKL is known to occur in the synovial membrane of chronically OA joints, leading to secondary bone resorption[39,100]. In similar context, another group recently investigated the expression of bone resorption genes in OA and OP, in relation to differences in RANKL regulation of proteases[101]. In this, cathepsin K, MMP-9 and tartrate resistant acid phosphatase (TRACP) mRNA were transcribed at higher levels per given RANKL expression in the OA group compared to that in the fracture (OP) group[101]. This may indicate that blockade of osteoclast formation may constitute a potential target in preventing the structural damage seen in OA. Novel monoclonal antibodies neutralizing the RANKL may prove interesting in preventing both OP and OA-associated bone loss, but at present clinical data are sparse. In alignment, the recently approved anti-resorptive strategy strontium ranelate, might in addition have beneficial effects on cartilage health, although the anti-resorptive effect compared to that of anti-RANKL, SERMs, calcitonin and bisphosphonates is lower[102].

This compilation of evidence suggests that bone and cartilage turnover are tightly associated, and that some selected anti-resorptive treatments may have additional benefits on cartilage health. Does this suggest that stimulation of bone formation may have adverse effects? Bone sclerosis is an important part of the pathogenesis of OA[103–107], that leads to deformation of the articular surfaces and absorption of local stresses producing an effect similar to stress-shielding that may augment OA progression. Recently wnt signaling was shown to be essential for osteophyte generation[40], and bone sclerosis in an animal model of cartilage destruction. In addition, upregulation of genes in the wnt family has also been observed[108]. Finally, there is evidence indicating that low-density lipoprotein receptor-related protein (LRP)5 haplotypes are associated with OA[109,110]. An increasing amount of attention is focused on bone anabolic drugs, with special emphasis on wnt enhanced signaling. Will these interventions be associated with augmented OA symptoms and disease progression? These important questions of safety need to be addressed in future studies specifically designed for that purpose.

Due to the unmet medical need and the widespread nature of OA, it is urgent to develop safe and effective disease modifying treatments for patients with OA. Ample evidence is found for a tight local coupling between bone and cartilage. Thus, an optimal treatment option for OA would entail both bone and cartilage protective effects. However, with this information limited options seem possible. Some estrogens compounds and calcitonin may provide this dual actions approach, however, still more clinical research is needed.

Conflict of interest

All authors declare that the affiliation declares full disclosure. In addition, MAK and CC own stock in Nordic Bioscience.

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