Review

Subchondral bone changes and the impacts on joint pain and articular cartilage degeneration in osteoarthritis

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ABSTRACT

Subchondral bone has received increasing attention in both basic and clinical research on osteoarthritis (OA). Subchondral bone in OA presents abnormalities in structure, biochemical composition, biomechanics and cellular function. Overall, subchondral bone mainly shows bone resorption in early OA and bone formation in late OA. More and more evidence suggests that abnormalities in subchondral bone of OA promote joint pain generation and articular cartilage degeneration. Inhibition or amelioration of subchondral bone abnormalities can reduce joint pain and can delay cartilage degeneration; thus, subchondral bone-targeted treatment promises to be a new treatment approach for OA. The pathological changes and the role of subchondral bone in OA still require further investigation.

Introduction

Osteoarthritis (OA) is the most common bone and joint disease. Its pathological features mainly include progressive loss of articular cartilage, changes in subchondral bones, mild synovial reaction and abnormalities in adjacent soft tissue. Chronic joint pain, especially weight-bearing pain, is a major clinical symptom of OA. Numerous studies in recent years have suggested that abnormal changes in subchondral bones of OA are closely related to joint pain and articular cartilage degeneration. This paper reviews and analyses the roles of subchondral bones in OA.

Anatomical structure and biological function of subchondral bone

Typically, subchondral bone refers to the subchondral bone plate and the subchondral trabecular bone distal to the calcified zone of the articular cartilage. The subchondral bone plate is between the calcified cartilage layer and the trabecular bone and consists of cortical lamellar bone, similar to cortical bone (1-3). Some scholars also define subchondral bone as the calcified structure distal to the tidemark of articular cartilage; the calcified cartilage layer is attributed to the subchondral bone plate (1, 4-6). Structures such as calcified cartilage, the subchondral bone plate and the trabecular bone might have different impacts on OA pathogenesis. However, current imaging technologies cannot distinguish these structures based on anatomy, and many clinical imaging studies are actually based on the observation of subchondral calcified tissue.

Under physiological conditions, subchondral bone may provide mechanical support for the articular cartilage, and, together with articular cartilage, transmit the intra-articular load. Subchondral bone can buffer approximately 30% of the intra-articular stress, can maintain the matching of the joint, and can prevent intra-articular stress concentration. In addition, it provides nutritional support for articular cartilage through the terminal vasculature in the bone plate and the calcified cartilage layer (2, 4, 7).

Pathological changes of subchondral bone in OA

One of the main features of OA is subchondral bone sclerosis, as revealed via imaging. However, this study shows that the manifestations of subchondral bone exhibit dynamic changes with OA disease progress, with mainly bone resorption in the early stages and bone formation in the late stages.

In the early or progressive stage of OA, subchondral bone exhibits signs of active remodelling. The subchondral bone mineral apposition rate is increased by 3–5 times (8, 9), and bone remodelling

sites are also increased; active bone remodelling reduces the subchondral bone plate thickness (10). Previously, using an anterior cruciate ligament transection (ACLT) model, it was observed that early-stage OA induces a significant reduction in the subchondral bone plate thickness and a significant increase in plate porosity (11). Observations based on the collagenase-induced mouse model of OA (12, 13) and the rat ACLT model (14) or combined with medial meniscectomy (ACLT + MMx) (15) all identified significant loss of subchondral bone plate and/or trabecular bone in the early stage of OA. Similar findings have also been reported in early OA patients (16, 17), and one study revealed that bone resorption markers were significantly increased in patients with progressive OA, but not in patients with non-progressive OA (18). In middle-aged and young male early-stage OA patients with no clinical symptoms, bone resorption markers were also elevated (19).

The causes leading to increased subchondral bone remodelling in early OA remain unknown. The possible mechanisms include repair of microscopic damage, vascular invasion induced by pro-angiogenic factors, and bone and cartilage interactions via micropores in the subchondral bone. Sustained intra-articular load can lead to microscopic cracks in the subchondral bone plate, and these microscopic cracks can initiate bone remodelling (20, 21). In OA, the production of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), is increased in bone and cartilage, angiogenesis is increased in subchondral bone, and blood vessels invade into the deep layer of the articular cartilage (22). It is well known that increased bone remodelling is associated with vascular invasion. Degenerative cartilage and subchondral bone present increased transforming growth factor beta (TGF-β), insulin-like growth factor 1 (IGF-1), interleukin (IL)-1, IL-6 and prostaglandin E2 (PGE2) levels, upregulated Wnt signalling, upregulated receptor activator of nuclear factor kappa-B ligand (RANKL) and downregulated osteoprotegerin (OPG) expression, which can stimulate bone remodelling (23-26). In normal joints, there are micropores in the subchondral bone plate, enabling interactions between subchondral bone and cartilage (7), while the porosity of the subchondral bone plate is increased in OA pathogenesis (13). Using tracer techniques, it has been observed that physiological interactions may occur between rat subchondral bone and articular cartilage (27). It has been demonstrated in two mouse models that cartilage damage and vascular invasion can increase the size and number of pores, allowing bone and cartilage interaction via small molecule diffusion (28, 29).

In the late stages of OA, bone turnover is reduced and bone resorption is decreased, while bone formation is relatively increased, resulting in the manifestation of subchondral bone plate sclerosis in imaging (26, 30, 31). The coupling mechanism between normal bone resorption and bone formation is disturbed in late OA, and the balance tilts toward bone formation (32). Multiple studies have shown that compared to the normal population, subchondral bone of late OA patients exhibits increased bone density, bone volume, and collagen content and decreased calcium to collagen ratio, bone mineralisation, and mechanical strength (33-36). This situation is caused by the difference between the apparent and material densities of bones. If the bone volume fraction is increased, the apparent density is also increased, while insufficient bone mineralisation leads to reduced material density and decreased mechanical strength. Studies have shown that the subchondral bone volume fraction and bone mineralization have a negative correlation in late OA, which is a process of co-adaptation, namely to increase bone mass in response to inadequate bone mineralisation (37).

The mechanisms by which subchondral bone mineralisation is reduced in late OA are not clear but may be related to osteoblast differentiation factors [38]. It has been revealed that reductions in bone mineralisation are related to increased production of TGF-β and Dickkopf WNT signalling pathway inhibitor 2 (DKK-2) in subchondral osteoblasts (39, 40). DKK-2 is the Wnt signalling inhibitor and can inhibit osteoblast mineralisation (41). Other studies have also shown that, under physiological conditions, type I collagen produced by osteoblasts consists of heterotrimers of 2 a2 chains and 1 a1 chain and that collagen produced by osteoblasts in late OA consists of a1 homotrimers, which can damage the normal mineralisation process of collagen (42).

In addition, with the development of medicine, magnetic resonance imaging (MRI) techniques have been wildly applied for the diagnosis and examination of articular OA. Subchondral bone marrow lesions (BMLs) are a characteristic feature of OA on MRI imaging, revealed as subchondral hypersignal areas with fuzzy boundaries in either T2-weighted fat suppression sequences or short tau inversion recovery sequences. In the histopathology, the manifestations of subchondral BMLs include oedema, fibrosis, bone necrosis, trabecular bone damage and bone remodelling (43). With the progression of OA, BMLs can present no significant changes, expand continuously, disappear or form new lesions (44, 45). Analysis based on MRI combined with microcomputed tomography (Micro-CT), quantitative CT (QCT) or dual-energy x-ray absorptiometry (DXA) revealed that in late OA, areas with subchondral BMLs present bone sclerosis, an increased bone volume fraction and reduced bone density in the tissue (46-48).

OA subchondral bone and joint pain

Chronic joint pain is a prominent OA symptom. The causes of pain and its treatment programs have remained major problems in orthopaedic basic and clinical research. Current studies suggest an important role of subchondral bone in the generation and treatment of joint pain in OA.

Many studies based on clinical imaging studies prove that subchondral bone abnormalities in OA are positively correlated with joint pain. Structural changes in the knees of OA patients on x-ray images (Kellgren and Lawrence grade) are significantly correlated with joint pain (49). Knee subchondral bone attrition (SBA) refers to the vertical bone loss or compression of the affected plateau and

is considered to be the manifestations of subchondral bone remodelling (17), a common imaging finding in patients with knee OA. SBA identified in knee x-ray and MRI images are strongly associated with joint pain (50, 51), and the degree of exposure of subchondral bone is positively correlated with joint pain (52). BMLs observed on MRI images are correlated with knee pain and can even predict joint pain better than synovitis (53, 54). Additionally, the occurrence or development of BMLs is associated with increased pain (45).

Histopathological studies have observed that pain sensory nerve fibers are distributed in the subchondral bone of normal joints (55), while the neurovascular bundles are increased in subchondral bone plates with OA and invade the osteochondral junction until the deep articular cartilage layer is reached (56-58). It has also been found that the production of a variety of inflammatory mediators and pain neurotransmitters is increased in OA subchondral bone (59). Using rat models of OA joint pain, it has been observed that injuries and changes can occur in the sensory neurons controlling the knee (60, 61).

Results of studies focusing on treatments targeting subchondral bone also support the notion that subchondral bone changes play an important role in the generation of joint pain. Some clinical studies have observed that bone protection drugs inhibiting bone resorption or promoting bone formation, such as bisphosphonates (62, 63), and strontium ranelate (64, 65), can ease joint pain in patients with OA by improving or inhibiting abnormalities in subchondral bone. Animal experiments in mice (66), rats (67-69) and dogs (70) also found that drugs for bone protection can improve the subchondral bone structure, reduce the behavior of joint pain, and reduce the expression of markers of pain.

There are several possibilities by which improvement in subchondral bone can mitigate joint pain. Under physiological conditions, articular cartilage is avascular and aneural (71), while subchondral bone is rich in blood vessels and nerves (72, 73). In addition, neurovascular bundles in the subchondral bone plate are increased and invade the bone cartilage interface in OA (56, 58). Due to changes in the structural and mechanical properties of subchondral bone in OA (74, 75) and the increased production of inflammatory pain-causing factors, pain receptors in the subchondral bone are vulnerable to chemical or mechanical irritation or injury (76), thereby presenting symptoms of OA pain, particularly weight-bearing pain (72). Therefore, improving the structural and mechanical properties of the subchondral bone can protect subchondral pain receptors from irritation or damage and can thus relieve joint pain. In addition, studies have shown that the acidic environment that results from the increased activity of osteoclasts can also lead to the generation of pain (77). In OA pathogenesis, subchondral bone turnover is active, and osteoclast activity is enhanced; thus, inhibition of osteoclast activity may also help reduce joint pain. In clinical practice, OA pain in the medial or lateral single compartment of the knee can often be effectively alleviated via high tibial osteotomy. This treatment adjusts the line of force of the knee, balances the intra-articular load, and reduces hyperstimulation on the cartilage and subchondral bone of the lesion side due to excessive stress (78). Unicompartmental or total knee replacement for the treatment of OA joint pain is already a mature operation in bone and joint surgery. This treatment removes diseased cartilage and subchondral bone and replaces articular friction pairs (79), which further indicates that subchondral bone is a major source of joint pain in OA.

Subchondral bone and articular cartilage degeneration in OA

Currently, whether changes in subchondral bone are the initiating factor or secondary changes for articular cartilage degeneration in OA is controversial. For a long time, subchondral bone abnormalities in OA have been considered secondary to degeneration of articular cartilage, which has been supported by many experimental studies (80, 81). However, other experimental studies have found that changes in subchondral bone can occur prior to or simultaneously with the occurrence of cartilage degeneration (82-85). In any case, it is certain that there is a correlation between changes in subchondral bone and the degeneration of articular cartilage; occurrence of subchondral bone abnormalities may accelerate cartilage degeneration, and improvement of bone abnormalities can slow down cartilage degeneration.

Using bone scintigraphy, it has been observed that enhanced subchondral bone turnover in patients with knee OA is related to rapid disease progression (16). Multiple imaging studies based on MRI have revealed that the loss of articular cartilage in OA is strongly related to subchondral BMLs and SBA (50, 52, 86-92), the loss of articular cartilage and subchondral bone resorption are correlated in anatomical positions (37), and the risk of articular cartilage loss is increased 7-fold in areas of SBA (92). Using a canine ACLT model (11) and a rabbit osteoporosis model of joint instability (93), it was observed that articular cartilage damage is related to a reduction in subchondral bone plate thickness. Experimental studies using mice and rabbits have shown that cartilage degeneration occurs in the bone plate-thickening region, and no degeneration occurs in the area without bone plate thickening (8, 94). There are a variety of animal models, such as type I collagen mutant mice (95), mice overexpressing Runt-related transcription factor 2 (RUNX2) (96), and osteoporosis rats (97) and rabbits (98, 99), confirming that increased subchondral bone turnover can promote the loss of articular chondrocytes and cartilage matrix, thus increasing articular cartilage damage.

In the mouse ACLT model, inhibition of excessive TGF-β1 levels in subchondral bone can improve bone structure and can slow down cartilage degeneration (100). Using genetically modified mice, it was observed that bone-specific over-expression of the osteogenic stimulator Ephrin type-B receptor 4 (EphB4) could protect subchondral bone in OA and could reduce articular cartilage damage (101). Multiple animal experiments demonstrated that inhibiting or improving subchon-

dral bone damage by the application of osteoprotective agents, such as the anti-bone resorption drugs of oestrogen, calcitonin, bisphosphonates and OPG, the pro-osteogenesis drug teriparatide, and the bidirectional regulation drug strontium ranelate, could slow down articular cartilage degeneration (14, 22, 66, 97, 98, 102, 103). In addition, a number of clinical trial results also support the positive roles of osteoprotective agents in inhibiting the degradation of cartilage type II collagen and delaying cartilage degeneration in OA (65, 104-107).

The mechanism by which subchondral bone affects articular cartilage degeneration remains unclear and may be related to the following two aspects. From the biomechanical point of view, articular cartilage contains a lot of water and has a strong capacity to withstand compressive stress but has weak capacities to withstand tensile and shear stress. Heterogeneities in the density and rigidity of subchondral bone in OA, along with reduced elasticity, result in abnormal tensile stress and shear stress towards articular cartilage, thus facilitating cartilage degeneration (108). From the aspect of molecular biology, the porosity is increased for the micropores in the subchondral bone plate of OA, interaction between bone and cartilage is strengthened (13, 29), and the subchondral osteoblasts, osteoclasts, and osteoblasts in OA can release a variety of proteases, inflammatory mediators and growth factors that can promote chondrocyte death in the upper layer and matrix degradation (109, 110).

Finally, it should be noted that, despite the growing number of animal and clinical experiments confirming that targeting subchondral bone via bone protective agents can relieve joint pain and can slow down articular cartilage degeneration, some clinical studies have also observed that the efficacy remains controversial (62). A main reason for this inconsistency may be that subchondral bone presents dynamic transitions in the course of OA and cannot always be suppressed or improved; therefore, the intervention effects rely on the initial treatment period (68).

Summary

In OA, subchondral bone presents dynamic changes in the course of the disease, mainly showing bone resorption in the early stage and bone formation in the late stage. More and more evidence proves that subchondral bone abnormalities in OA promote the occurrence of joint pain and articular cartilage degeneration. With the gradual deepening of our understanding of subchondral bone in OA, therapies targeting subchondral bone could become a new treatment in clinical practice.

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