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Research Progress on Subchondral Bone Lesions in Knee Osteoarthritis

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Abstract: This article reviews the research on subchondral bone lesions in knee osteoarthritis. Subchondral bone is closely related to articular cartilage in terms of embryonic development and anatomical structure, and the two form bone-cartilage units. These units interact and crosstalk with each other in biomechanics and molecular biology. Subchondral bone lesions include various pathological forms. There are certain research prospects for the prevention and treatment of knee osteoarthritis targeting the subchondral bone.

Keywords: Knee osteoarthritis; Subchondral bone; Bone-cartilage unit

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1. Introduction

Knee osteoarthritis (KOA) is a disease characterized mainly by the degeneration of articular cartilage. With the aging of the population and the increase in the number of obese people, the number of KOA patients has increased, which has brought a great burden to society and families [1,2]. Drug and non-drug treatments for KOA can effectively relieve joint pain, but they cannot effectively reverse the pathological process of KOA. As the severity of the disease increases, it can cause significant pain and joint function limitations, and in severe cases, surgical treatment is required [3]. KOA is currently also regarded as a disease of the entire joint, in which subchondral bone is closely related to articular cartilage. Studies have shown that the integrity and homeostasis of articular cartilage may depend on the biomechanical and molecular biological interactions with subchondral bone [4]. There are certain research prospects for the prevention and treatment of KOA through the regulation of subchondral bone.

2. Embryonic development and tissue structure of subchondral bone

The femur and tibia in the knee joint originate from bone marrow mesenchymal stem cells in the embryo.

These stem cells form "blastema," which contains a small amount of type I collagen matrix and transforms into a cartilage structure in the early fetal stage. The extracellular components of this structure are mainly type II collagen [5]. During the terminal differentiation of cartilage, it hypertrophies and forms blood vessels and bone mineralization, thereby causing the process of endochondral ossification and creating the main ossification center. After birth, three cartilaginous interfaces are formed at the tibia and femoral ends of the knee joint, namely the chondroepiphyseal bone, the growth plate epiphyseal bone, and the growth plate metaphysis bone. The articular cartilage is located at the top of the subchondroepiphyseal bone. During growth and development, the epiphyses expand into the chondroprimordium until a very thin calcified layer is formed deep within the cartilage, thus forming calcified cartilage. The perivascular bone beneath the calcified cartilage gradually deposits to form subchondral bone plates and the supporting trabeculae below. At this stage, a wavy structure forms at the junction of the cartilage and the subchondral bone. This is conducive to the close combination of the two and the dispersion of the stress in the upper cartilage [6]. From the perspective of embryonic development and anatomical structure, cartilage and subchondral bone have a close relationship and may influence each other pathologically.

3. Bone-cartilage units and KOA

Bone and articular cartilage form the "bone-cartilage unit," which includes hyaline cartilage, hyaline line, calcified cartilage, and subchondral bone. This unit is a complex functional unit. There is mutual interference between molecules at the junction of articular cartilage and subchondral bone. Abnormal remodeling of subchondral bone caused by KOA can lead to vascular and nerve invasion of the junction area between articular cartilage and subchondral bone. Cartilage damage and vascular invasion can increase the diffusion of small molecules in this area and enhance the cross-interference between articular cartilage and subchondral bone molecules [7,8]. In terms of biomechanics, abnormal subchondral bone remodeling caused by KOA, such as bone destruction, bone sclerosis, and thickening of subchondral bone plates, may damage the mechanical characteristics of subchondral bone, leading to the loss of mechanical balance between cartilage and subchondral bone, thereby aggravating the degeneration of overlying articular cartilage [9].

4. Manifestations and treatment of subchondral bone lesions in KOA

4.1. Subchondral bone destruction

Animal studies have shown that in the early stage of KOA, the activity of osteoclasts in subchondral bone increases, leading to subchondral bone resorption and the formation of a large number of cavities. Osteoclasts can also secrete netrin-1, which promotes the innervation of sensory nerves in subchondral bone, thereby aggravating joint pain [10]. Studies have found that in the early stage of KOA, the expression of prostaglandin E2 (PGE2) in subchondral bone and prostanoid 4 (EP4) in osteoclasts increases. PGE2 can promote the differentiation of osteoclasts through EP4, causing the destruction of subchondral bone structure and sensory nerve innervation related to pain [11]. Not all animal studies showed enhanced activity of osteoclasts in the early subchondral bone of KOA. Studies found that in the same mouse, through the left knee anterior cruciate ligament transection to simulate KOA, in the early stage, the subchondral bone of the left knee joint shows enhanced osteoclast activity, while the right knee joint on the opposite side only shows weak osteoblast changes. This may be somewhat different from the spontaneous KOA in humans [12]. This also indicates that

the enhanced activity of subchondral osteoclasts in the early stage of KOA in animal studies may be related to the abnormal load caused by mechanical damage resulting from surgical modeling. Zoledronate belongs to the bisphosphonate class of drugs and has the effect of inhibiting osteoclast generation. Zoledronate can alleviate the early subchondral bone mass loss in KOA rabbits, thereby improving the bone microstructure and alleviating the degeneration of articular cartilage [13]. Clinical studies have also found that zoledronate can alleviate joint pain and limited joint movement in patients with KOA, and can reduce the use of non-steroidal anti-inflammatory drugs [14]. Some studies have found that the preventive use of alendronate can alleviate the early subchondral bone destruction of KOA and relieve cartilage degeneration. Although the use of alendronate two weeks after modeling can reduce subchondral bone destruction, it cannot effectively relieve cartilage degeneration [15]. Because the main mechanism of bisphosphonate drugs is to inhibit the activity of osteoclasts, the timing of treating subchondral bone lesions in KOA is crucial. However, if the cartilage has already undergone degeneration, while the use of bisphosphonate drugs at this time can alleviate abnormal bone remodeling, the damage to the cartilage is already irreversible.

4.2. Subchondral bone sclerosis

As KOA progresses and subchondral bone undergoes continuous bone remodeling, subchondral bone gradually thickens and its bone density increases, leading to subchondral bone sclerosis [16]. Stromal cell-derived factor-1α (SDF-1α) is closely related to bone metabolism. In KOA mice, SDF-1α in subchondral bone and peripheral blood slightly increased in the second week after modeling, but significantly increased in the eighth week. High levels of SDF-1α promote the proliferation of bone marrow mesenchymal stem cells, thereby indirectly leading to an increase in osteoblast differentiation and bone formation, and causing subchondral bone hardening [17]. Transforming growth factor-β (TGF-β) is a key factor for maintaining the normal structure of articular cartilage, but it is also involved in the pathological process of KOA. Abnormal remodeling of subchondral bone in KOA can cause an increase in the production of TGF-β, leading to degeneration of articular cartilage and excessive osteogenesis [18]. Vasoactive intestinal peptide (VIP) is related to bone metabolism. VIP can promote osteogenic formation. The expression of VIP in subchondral bone significantly increases in patients with severe KOA. The use of VIP antagonists in KOA mice can alleviate the hardening of subchondral bone and the degeneration of articular cartilage [19]. Metformin is a hypoglycemic drug, but it can also affect bone metabolism through its anti-inflammatory effect. Research has found that metformin can alleviate the degeneration of cartilage in KOA mice and also reduce the hardening of subchondral bone, thereby exerting a therapeutic effect on KOA [20]. Compared with drug treatment, physical therapy may have more research prospects. Some studies have found that low-intensity ultrasound can reduce cartilage degeneration and repair cartilage, as well as alleviate the hardening of subchondral bone [21].

4.3. Subchondral bone marrow lesions

Bone marrow lesions (BMLs) are the imaging features of the subchondral bone region of the knee joint on MRI, manifested as low-signal areas in T1-weighted images and high-signal areas in T2-weighted images. BMLs include pathological changes such as subchondral bone marrow edema, hemorrhage, necrosis, and bone remodeling, which are seen in diseases such as fractures, bone contusions, and KOA. Therefore, BMLs are not a specific manifestation of KOA, but there is a significant positive correlation between BMLs and articular cartilage injury. Moreover, BMLs can occur in the early stage of KOA, even before articular

cartilage degeneration [22,23]. A study has found that after a 3-year follow-up, the proportion of total knee arthroplasty in KOA patients with BMLs was significantly higher than that in patients without BMLs. Moreover, the larger the range of BMLs in KOA patients, the higher the proportion of total knee arthroplasty. This also indicates that BMLs are one of the risk factors for the progression of KOA [24]. In terms of treatment, injecting calcium phosphate into the BMLs of KOA patients can alleviate joint pain and improve joint function, but the impact on patients' long-term prognosis remains uncertain. In patients with KOA, the increase in the range of BMLs is closely related to the aggravation of joint pain. After neridronate injection treatment is given to patients with acute joint pain and BMLs in KOA, the BML score can be reduced and joint pain can be improved [25].

5. Conclusion

Subchondral bone and articular cartilage form the bone-cartilage unit, and the two are closely related in physiology and pathology. The lesions of subchondral bone in KOA can be observed in animal studies as abnormal activation of osteoclasts in the early stage and abnormal osteogenesis in the late stage leading to subchondral bone hardening. However, whether there is abnormal activation of osteoclasts in the subchondral bone of early KOA in humans requires further research. The BMLs of subchondral bone are closely related to the progression of KOA disease. The treatment of KOA by targeting BMLs has certain research prospects.

Disclosure statement

The authors declare no conflict of interest.

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