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Perspective Article

Clinical aspects, pathology and pathophysiology of osteoarthritis

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Osteoarthritis (OA) is the most common joint disorder, and there is evidence that a majority of individuals over the age of 65 have radiographic and/or clinical evidence of OA. The most frequently affected sites are the hands, knees, hips and spine. Importantly, the symptoms are often associated with significant functional impairment, as well as signs and symptoms of inflammation, including pain, stiffness and loss of mobility[1]. Anatomic analysis and application of histopathological and imaging techniques have helped to define the natural history of OA with respect to the structural alterations in the articular cartilage[1-6]. They also have demonstrated that OA is not exclusively a disorder of articular cartilage. Multiple components of the joint are adversely affected by OA, including the peri-articular bone, synovial joint lining and adjacent supporting connective tissue elements[1-6].

The characteristic structural changes in OA include the progressive loss of articular cartilage, increased subchondral plate thickness, formation of new bone at the joint margins (osteophytes) and the development of subchondral bone cysts[7-9]. In addition, at the junction of the articular hyaline cartilage and adjacent subchondral bone, in the region of the so-called tidemark, there is a remnant of calcified cartilage. As OA progresses, there is evidence of vascular invasion and advancement of this zone of calcified cartilage into the articular cartilage that further contributes to a decrease in articular cartilage thickness[2,10-14]. These structural alterations in the articular cartilage and peri-articular bone may lead to modification of the contours of the adjacent articulating surfaces[7-9,15,16]. These changes, as well as the accompanying alterations in subchondral bone remodeling and modulus, may further contribute to the development of an adverse biomechanical environment and enhance the progression of the articular cartilage deterioration[15-19].

Multiple factors have been shown to affect the progression of OA, including the presence of polyarticular disease, increasing age, associated intra-articular crystal deposition, obesity, joint instability and/or malalignment, muscle weakness and peripheral neuropathy[1,20-22]. These factors can be segregated into categories that include hereditary contributions, mechanical factors and the effects of ageing.

There are several lines of evidence indicating that genetic factors contribute to the risk of OA[23,24]. These include the results of epidemiological studies, analysis of patterns of familial clustering, twin studies and the characterization of rare genetic disorders. For example, twin studies have shown that the influence of genetic factors may approach 70% in certain skeletal sites. Linkage analyses and association studies have implicated the involvement of several genes, including the vitamin D receptor, insulin-like growth factor, fibroblast growth factor, transforming growth factor and several cartilage matrix proteins. Interestingly, there is evidence that the genes may operate differently in males and females and at different body sites.

The articular surface plays an essential role in load transfer across the joint and there is good evidence that conditions that produce increased load transfer and/or altered patterns of load distribution can accelerate the initiation and progression of OA[27,28]. For example, Englund and Lohmander[29] examined the risk factors for symptomatic OA 15 to 22 years after meniscectomy in a Swedish cohort. They found that partial meniscal resection (which produced less disruption in the local biomechanical knee environment) was associated with a lower rate of radiographic progression than total meniscectomy. They also observed that risk factors for OA initiation and progression were similar to those for idiopathic OA in that systemic and local biomechanical

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factors interact and that obesity, female sex and pre-existing early-stage OA contributed significantly to an adverse radiographic and clinical OA outcome.

Whereas it is clear that mechanical and genetic factors play major roles in determining the natural history of OA, the primary risk factor for OA is age[30]. The aging process contributes to OA pathogenesis in several ways. The first relates to the influence of the ageing process on the structural organization and material properties of the cartilage extracellular matrix (ECM)[31-35]. There is evidence that the major components of the ECM, which consists of type II collagen and proteoglycan, undergo structural changes during the ageing process[33]. For example, aggrecan, which is the major cartilage proteoglycan, decreases in size and structural organization and its content in the ECM diminishes, likely contributing to an alteration in the biomechanical properties of the matrix. In addition, there is evidence of accumulation of advanced glycation end products (AGEs)[35]. This process has been shown to enhance collagen cross-linking and likely is a significant contributing factor to the increase in cartilage stiffness and altered biomechanical properties that has been observed with ageing.

The chondrocyte is the only cell type inhabiting the cartilage matrix. This cell is relatively metabolically inert and has little regenerative capacity. There is evidence that its capacity to remodel and repair the cartilage ECM diminishes with age, and this appears to be related primarily to a decreased anabolic capacity[32,36]. This may in part be related to the diminished capacity of the chondrocyte to respond to anabolic stimuli such as insulin-like growth factor. The effects of synovial inflammation likely contribute to dysregulation of chondrocyte function in an analogous fashion, favoring a disequilibrium between the catabolic and anabolic activities of the chondrocyte in remodeling the cartilage ECM[37-40].

Essential to the development of more effective strategies for treating patients with OA and in altering the natural history of this disorder, is an understanding of the cellular processes that regulate the functional activities of chondrocytes in both physiological and pathological conditions. Improved techniques for monitoring the effects of therapeutic interventions on the structural and functional properties of cartilage matrix also are needed. In addition, further insights into the role of peri-articular bone remodeling and synovial inflammation on the natural history and outcomes in OA are necessary. Finally, more information is needed regarding the origin of pain and related symptoms in OA, since there is already a large segment of the population who are significantly disabled and suffering from this common joint disorder.

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