

# Osteoarthritis physiopathology: review article

## Summary

Osteoarthritis is a progressive joint disease of complex etiopathogenesis. It compromises the joint as a whole, generating pain and disability, especially in ageing people, the most affected age group. The purpose of this study is to discuss the etiology and the main risk factors involved in the pathophysiology of this disease. The review included articles published in journals indexed in the Embase, Pub Med and UpToDate databases. Its pathophysiology involves the involvement of any joint structures in addition to defects in the repair of damaged cartilage and the influence of mechanical and biochemical factors. Full knowledge of the pathophysiology of OA can mean a revolution in its treatment.

**Keywords:** osteoarthritis, etiology, risk factors

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## Introduction

Osteoarthritis (OA) is considered a progressive joint disease caused by failure to repair joint injuries.<sup>1</sup> This pathology is considered the most common form of arthritis, it is a major public health problem, as well as being the major responsible for pain and disability in the elderly.<sup>2,3</sup> Due to the longer life expectancy and increased obesity, it is estimated that from 2000 to 2020 disease prevalence will double.<sup>4,5</sup> The WHO rheumatic disease scientific group estimated that 10% of the world population aged 60 years or older had significant clinical problems attributable to OA.<sup>5</sup> Any articular structure may be involved, including articular cartilage, subchondral bones, ligaments, meniscus, periarticular tissues, peripheral nerves, and synovium.<sup>1</sup> The joints most affected by osteoarthritis, in turn, are those of the knees, hips and hands.<sup>6</sup> Half of those aged 50 or older report having knee pain for a year, and one-fourth have severe and disabling pain. This picture of knee pain can lead to a significant reduction in the ability to perform daily activities.<sup>7</sup> In the pathogenesis, at the molecular level, increased activity of cytokines and chemokines contributes to the inflammatory component of osteoarthritis, responsible for the destruction of cartilage.<sup>8</sup> Intra-articular stress and repair failure can be generated by biomechanical, biochemical and/or genetic factors. Almost half of the patients with radiological features of osteoarthritis have no symptoms and vice versa. The risk factors for the occurrence and progression of the disease differ according to the involved joints.<sup>6</sup> This study aims to review relevant aspects of the pathophysiology of osteoarthritis, the mechanism of which is not fully understood, despite the high prevalence of the disease.

## Method

The literature review focused on indexed journals in the Embase, PubMed and UpToDate databases. The keywords used in the English search were: Osteoarthritis, Pathophysiology of osteoarthritis, Risk factors for osteoarthritis. The inclusion criterion was all the recent articles that addressed the subject.

## Discussion

### Pathophysiology

Osteoarthritis was once considered only a degenerative disease, since the main component of OA is the destruction and loss of articular

cartilage.<sup>1,9</sup> Its etiopathogenesis is more complex and includes the involvement of other joint structures, besides defects in the repair of damaged cartilage and the influence of mechanical and biochemical factors.<sup>2,6,9</sup> The sequence in which the joint tissues are affected is related to initiation factors. It is usually difficult to identify the exact component that was affected first, with the exception of posttraumatic OA. The evolution of the disease results in the compromise of the whole joint. However, the progression of OA does not occur at the same intensity for all patients and only a portion will progress to the more advanced stages of the disease. Therefore, identifying those patients who will reach the final stages of OA is still a challenge.<sup>9</sup> Classical cell inflammation is not significant in osteoarthritis. The number of leukocytes present in the joint fluid is usually low, and hardly exceeds 1000 to 2000 cells/mL. The inflammatory component of Osteoarthritis is better characterized by the presence of several proinflammatory mediators, including cytokines and chymotrypsins, components of the innate immune response of the joint injury that stimulate the production of proteolytic enzymes, which degrade the extracellular matrix, destroying the articular tissue.<sup>9</sup> The articular cartilage, through the production of hyaluronic acid and lubricin by the chondrocytes and synovial cells, guarantees a smooth surface with a very low coefficient of friction, which allows efficient sliding during the joint movement.<sup>2</sup> Thus, another hypothesis to explain how OA starts is through an increase in the coefficient of friction caused by loss of lubricant in the synovial fluid.<sup>7</sup> Increased friction between cartilage surfaces would increase the shear force on the surface of the cartilage, affecting the metabolic function of the chondrocytes and their survival. In addition, increased friction, loss of proteoglycan from the cartilaginous matrix and death of chondrocytes promotes a progression of the disease. However, there is no proven direct link between attrition and chondrocyte apoptosis.<sup>10</sup> As articular cartilage has no innervation, the changes do not produce clinical signs. The synovial inflammatory process is responsible for clinical symptoms such as: joint edema, inflammatory pain. Synovial macrophages produce catabolites and pro-inflammatory mediators, causing an imbalance between the degradation and repair of the cartilaginous matrix. The main features of OA arise from alterations in the subchondral bone, since the formation of osteophytes, bone remodeling and subchondral sclerosis occur at the onset of the disease, even before the cartilaginous degradation. This leads to the hypothesis that the subchondral bone could initiate cartilage damage.<sup>6</sup>

## Articular components

### Joint cartilage

Initial pathological changes in OA are commonly observed on the surface of articular cartilage with fibrillation in focal regions that support maximum load. First, the cartilage becomes swollen, as the collagen web releases the hydrophilic proteoglycans, attracts water and expands. Chondrocytes, the only type of cell present in cartilage, preserve the cartilaginous structure through normal anabolic/catabolic activities.<sup>9</sup> With the development of OA the chondrocytes proliferate rapidly, forming agglomerates, in an attempt to repair damaged areas and increase the concentration of matrix growth factors.<sup>6,9</sup> A portion of these cells transforms into hypertrophic chondrocytes, similar to cells found in the hypertrophic zone of the growth plate that produces type X collagen and metalloproteinase-13 (MMP-13). Studies have shown that chondrocytes in OA reproduce some of the differentiation processes that occur during embryogenesis. In the growth plate development process, hypertrophic chondrocytes express type X collagen and matrix metalloproteinases (MMPs), which subsequently induce cartilage degradation as part of the endochondral ossification process. The degradation of cartilage on the growth plate resembles the cartilaginous degeneration occurring in the AO, also mediated by MMPs.<sup>11</sup> The extensive degradation of the matrix is due to the continuous production of proteases driven by pro-inflammatory cytokines and fragments of matrix proteins, which stimulate chondrocytes to produce more cytokines and proteases.<sup>9</sup> The expressive damage in the matrix causes chondrocyte apoptosis, resulting in matrix areas without the presence of cells.<sup>5,9</sup>

The main components of the extracellular matrix of articular cartilage, produced by chondrocytes, are aggrecan and type II collagen.<sup>12</sup> Collagen is responsible for tensile strength, while aggrecan adsorbs water to the interior of the matrix, conferring resistance to compression.<sup>13</sup> The decrease of aggrecan from the reduction of its synthesis by chondrocytes and the activation of enzymes that degrade the cartilaginous matrix, belonging to the family of disintegrin and metalloproteinase with thrombospondin motif (ADAMTS), are the first events in the course of Oz.<sup>14,15</sup> Studies suggest that MMP-13 is predominantly responsible for the degradation of type II collagen. Although cartilage has a restricted ability to repair itself, aggrecan molecules can be resynthesized after enzymatic depletion and restoration of the mechanical properties of the tissue, but as long as there is no destruction of the collagen network. Once the collagen network ruptures, irreparable lesions are established in the cartilage, resulting in progressive loss.<sup>15</sup> The vascularization of the articular cartilage may be related to the symptoms in OA, since it allows the growth of sensory nerve in the normally aneural articular cartilage.<sup>16</sup> In regions where this vascular invasion occurs there is a replacement of the bone marrow by fibrovascular tissue expressing vascular endothelial growth factor (VEGF).<sup>2</sup> Certain mediators of OA such as metalloproteinases (MMPs), TNF, Toll-Like receptors (TLR) and p38 MAP kinase signal are also associated with neural mechanisms of chronic joint pain.<sup>3</sup>

### Bone

Bone remodeling can be initiated in regions of bone damage resulting from repetitive over-loading. This leads to the appearance of microcracks, which initiate segmented remodeling, contributing to bone marrow lesions observed in magnetic resonance imaging of patients with OA. Histological examination of the lesions shows

necrosis of the local fat and fibrosis of the marrow at various stages of healing.<sup>2</sup> The increase in the production of collagen implies in the thickening of the subchondral bone.<sup>9</sup> Osteophyte formation is linked to local production of growth factors such as transforming growth factor beta (TGF- $\beta$ ) and bone morphogenetic protein 2 (BMP-2). The role of the osteophyte is not fully elucidated, but is believed to contribute to joint stabilization rather than influence the progression of the disease. With the progression of the disease, bone cysts form, but erosion is not commonly observed, except for erosive OA that occurs in the distal joints of the hands (distal and proximal interphalangeal).<sup>2</sup>

### Sinóvia

The synovia contributes to the maintenance of healthy articular cartilage.<sup>16</sup> In turn, cartilage can modulate the function of the diseased synovial membrane.<sup>5</sup> These two structures are very close together, so there is a free flow of solutes between the two. Synovitis present in OA encompasses several abnormalities, including synovial lining hyperplasia, infiltration of macrophages and lymphocytes to the synovial membrane, neoangiogenesis and fibrosis.<sup>16</sup>

Synovia often develops hyperplasia of lining cells and under some circumstances undergoes infiltration of inflammatory cells. The activation of the synovium promotes secretion of excess synovial fluid, causing capsular edema. This edema, through spinal reflex, inhibits the complete activation of the periarticular muscles and this, associated with disuse, causes muscle weakness and atrophy.<sup>4</sup>

### Soft tissue

Tissues such as the ligaments, joint capsule, muscles and menisci are also affected by OA. The thickening of the joint capsule associated with osteophytes leads to the widening of the joint of OA.<sup>9</sup> Lesions of meniscus and/or articular ligaments predispose the development of OA. The pathological changes occurring in the meniscus, either by age or OA, are similar to those observed in articular cartilage, matrix rupture, fibrillation, calcification and cell death. An increase in vascular penetration followed by an increase in sensory nerve density was observed in menisci of patients with OA, which may be correlated with the capacity of the menisci to be a source of knee OA pain.<sup>2</sup>

### Risk factors

Among the risk factors for the different manifestations of osteoarthritis are: aging, obesity, altered biomechanics, trauma, underlying anatomical alterations, previous joint injury and genetic influences.<sup>2,8,17,18</sup>

### Obesity

Several studies have evidenced the association between obesity and the development of osteoarthritis in the lower limbs. Obesity is linked to greater severity in cases of OA in the knees and hip. A recent study has shown that those patients with high body mass index (BMI) and with osteoarthritis in the hip needed surgery with prosthesis placement more frequently and earlier. In experiments using OA-affected cartilage, it was observed that by applying excessive mechanical stress the chondrocytes started to release pro-inflammatory mediators and promoters of degradation, responsible for inflammation of the joints and breaking of the cartilaginous matrix. For a physical stimulus to generate biological effects requires the involvement of mechanoreceptors and a molecular cascade to convert the signal from mechanic to biochemist. Adipose tissue exhibits endocrine characteristics and releases soluble mediators to the systemic

circulation such as adiponectin, leptin and visfatin, which can act on both the overweight and overweight joints. This triggers immune and inflammatory responses. Serum levels of adiponectin may predict the radiographic progression of osteoarthritis in the hands.<sup>17</sup>

## Aging

Aging causes changes in the cartilaginous matrix and senescent chondrocytes, which contributes to the development of OA. Recent studies are demonstrating that aging acts on other joint tissues as well, such as meniscus, ligaments, bones and perhaps synovium.<sup>19</sup>

## Genetics in osteoarthritis

The most consistently confirmed genetic association is the FRZB gene polymorphism that raises the risk of hip OA in females.<sup>4,20</sup> A mutation in OA-related FRZB does not inhibit Wnt signaling, providing further translocation of beta-catenin to the nucleus and activation of transcription factors that amplify the production of metalloproteinase or destruction of cartilage.<sup>4</sup> It has also been shown that a functional variant (v158m) of the COMT gene, which codes for catechol-o-methyltransferase, is linked to hip pain in patients with OA in this region.<sup>21</sup> In addition, a single nucleotide polymorphism (SNP) was identified in the SCN9A gene (encoding the sodium channel 9 alpha subunit), which when present in patients with OA is associated with high scores on pain scores compared to control patients.<sup>20</sup> This SCN9A SNP confers change in the amino acid R1150W associated with the various pain modalities and with altered thresholds.<sup>21</sup> The rs6746030 is the SNP that results in changes in the level of pain in OA. Its recessive allele is associated with increased pain perception.<sup>22</sup>

## Conclusion

Due to the impact generated by OA in the elderly population the full understanding of its pathophysiology could revolutionize its therapy, allowing approaches that delay progressive joint destruction and avoid permanent functional impairment. It is worth noting, the need to minimize modifiable risk factors, to reduce the progression of the disease.

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## Conflict of interest

Author declares that there is no conflict of interest.

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