

# Influences in degenerative joint pathology

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## ABSTRACT

Improving the aged population's health is a complex goal that requires a multifactorial approach and the knowledge of etiopathogenic factors. Osteoarthritis is the most common joint disease and the second leading cause of disability in people over the age of 50, which has a substantial economic impact and turns into a real social and public health problem. Although it manifested in less than 30% of the older population, pathological changes in the articular cartilage are founded in all deaths over 65 years. That is why we consider primary prophylaxis an important goal for the disease. This minireview presents etiological factors as genetic predisposition, age, body mass index, sex, bone density and the pathogenic degradation of articular cartilage. This includes two aspects of evolution, the progressive degradation of the articular cartilage and the reparative reaction of the subchondral bone. In conclusion, knowing these mechanisms are the first step in managing degenerative joint pathology.

**Keywords:** degenerative joint pathology, osteoarthritis, knee joints, hip joints, hand joints, spine joints

## INTRODUCTION

Worldwide life expectancy increased by five years between 2000 and 2015, which led to an increase in the elderly population, considered over 65 years old. Increasing life expectancy at birth must be accompanied by maintaining the functional status of the elderly. This goal also includes a prophylactic approach to chronic degenerative diseases by identifying and combating the risk factors associated with these diseases (1).

The EU population will continue to age in the baseline scenario of the latest Eurostat population projections (2). This can be illustrated by the age dependency ratio, defined as the ratio of the number of older people (65 years and over) to the number of people considered to be of working age (15-64 years) (3).

The EU's elderly dependency ratio is projected to be 57% in 2100, almost double 2019 (31%). This means that there will be less than two people considered working age for every person over the age of 65. The projected increase in the dependency ratio in old age follows the trend observed in the last decade (26% in 2009, 31% in 2019, 57% in 2100) (2).

Healthy aging means maintaining the functional capacity of people for as long as possible and in old age. Chronic illness, infirmity, mental illness, and physical disability tend to become prevalent with age, leading to a decline in the quality of life of those affected. Improving the population's health is a complex goal that requires a multifactorial approach.

The generic term for osteoarthritis brings together several suffering of the joints, of degenerative cause, having as a common feature the destruction of the articular cartilage, followed by changes of all the structures in the joint composition. The consequences of these reshaping of the joint components are pain, obstruction of normal movements, and deformities (4).

Virtually any joint can be affected by the arthritic process, but with predilection, the most commonly requested joints: knees (gonarthrosis), hips (hip osteoarthritis), spine (spondylarthrosis), and finger joints.

Osteoarthritis is the most common joint disease and the second leading cause of disability in people over the age of 50, after coronary heart disease, which has a substantial economic impact and turns into a real public health problem. (5).

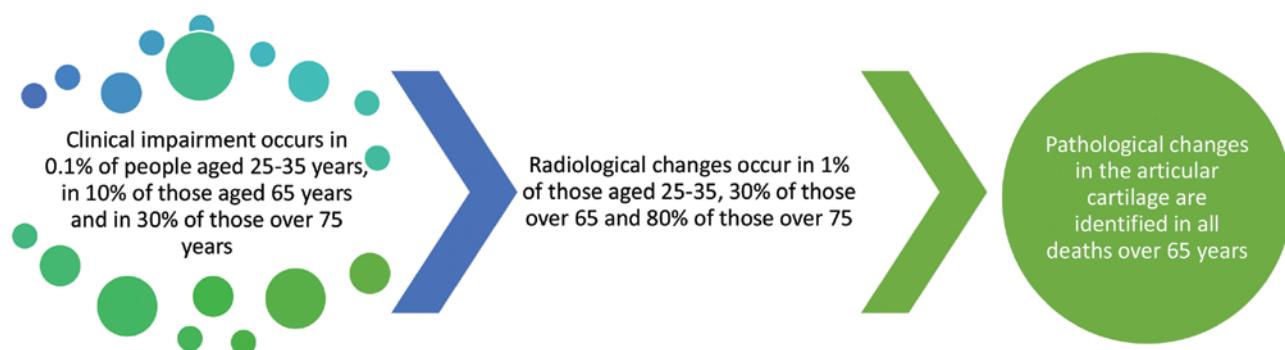


FIGURE 1. Average incidence (6,7)

Its incidence increases with age, being maximum between 55 and 75 years. Statistical data differ from study to study, but on average, it can be seen in Figure 1.

Up to the age of 65, the disease has an equal incidence by sex. After this age, it is two times more common in women, except for the location in the hip, the only one considered more common in men (1).

The preferred location of the arthritic process is at the level of diarthrodial joints, joints with high mobility, in the functioning of which cartilage plays an important role, such as the knee, hip, hand, spine joints (8).

## THE IMPACT OF ETIOLOGICAL FACTORS

From this point of view, osteoarthritis does not differ from inflammatory rheumatic diseases because its etiology is not known. However, many contributing factors have been identified, which have been divided into two categories: factors that determine a general predisposition to the disease and factors that determine local biomechanical anomalies.

The factors that determine a general predisposition to the disease are multiple.

Heredity is a family aggregation of the disease, proven by family studies and monozygotic twins, and this is more evident for polyarticular forms and osteoarthritis of the hand. The interest is polygenic, probably in the genes that ensure the synthesis of collagen and proteoglycans, and the transmission is autosomal dominant (9).

Age - as we have shown, the incidence of the disease increases with age. Some consider this a physiological process of aging cartilage, as is the case with any tissue in the body, even launching the term "cartilage failure." However, osteoarthritis is more than that, which is supported by the observation that joint changes due exclusively to age differ from those in osteoarthritis (10).

Sex - after menopause, women are twice as likely to get the disease; the prevalence is higher in hys-

terectomized women, while women who take estrogen hormone replacement have a lower incidence of osteoarthritis than those who do not take such therapy. This is especially evident for polyarticular forms, and these observations do not have clear evidence. Estrogen receptors have been shown on the surface of osteoblasts, and in vitro studies have shown that estrogens alter chondrocyte cultures (11).

Obesity - the question has arisen as to whether osteoarthritis, due to the hypomobility and sedentary lifestyle it induces, favors obesity or whether obesity favors the appearance of osteoarthritis (10). Numerous studies show that reducing body weight slows down the process of osteoarthritis. The association between osteoarthritis and obesity is more evident in women and is mainly related to the location at the knee (where it causes bilateral damage), less the hip and hands (12). A reduction in body weight by 5 kilograms reduces the risk of developing symptomatic gonarthrosis by 50%. In addition to mechanical overload, many metabolic factors contribute to osteoarthritis in obese patients, making obesity a systemic risk factor (4).

Bone density - there is a negative association between osteoporosis and osteoarthritis. It has been hypothesized that low bone density in the subchondral bone supports overload better than normal bone. Also, diseases associated with high bone density, such as Paget's disease or osteopetrosis, are associated with an increased frequency of osteoarthritis, with polyarticular and early damage (13).

Hypermobility - very mobile joints are most affected by the arthritic process.

Other diseases associated with an increased frequency of osteoarthritis are diabetes, hyperuricemia, hypertension (14).

Regarding the second category of favoring factors, the local ones, two situations predispose to osteoarthritis: abnormal stress of normal tissues and normal stress of abnormal tissues (8).

Abnormal stress on normal tissues is caused by repeated mechanical stress, abnormally exerted on the joint surface unit, due to excessive mechanical

forces: repeated physical exertion, movements related to the professional activity (occupational arthropathy), sports activity, obesity, static abnormalities (15). Injuries to the knees can lead to rupture of the cruciate ligaments, meniscus, altered cartilage, and predisposition to osteoarthritis from an early age. After meniscectomy, up to 89% of patients develop gonarthrosis (16). Fractures, subluxations, dislocations, by changing the normal ratios in the joints, also affect the mechanical function and promote osteoarthritis (17).

The normal stress of abnormal tissues is caused by primitive alterations of cartilage and joints: hip dysplasia, congenital hip dislocation, acetabular dysplasia, femoral condyle dysplasia, Blount's disease (aseptic necrosis of the medial tibial condyle or congenital hemiatrophy of the ep higher) (18) etc. Secondary alterations of the articular cartilage: after infectious, inflammatory, metabolic, endocrine, neurological diseases (7).

## **DEGRADATION OF ARTICULAR CARTILAGE AND THE REPAIR OF SUBCHONDRAL BONE**

The pathogenic process at the level of the articular cartilage mainly includes two aspects, the progressive degradation of the articular cartilage and the reparative reaction of the subchondral bone.

In the initial stages, the first change consists of the quantitative and qualitative alteration of the chondrocyte metabolism, especially in the synthesis of the extracellular matrix components, which alters the extracellular matrix properties. There is a switching of chondrocyte synthesis from the normal synthesis of type II collagen (characteristic of a mature chondrocytic phenotype) to type I, III, IX, and X collagen (which characterizes an immature chondrocyte phenotype) (19).

The first biochemical consequence is damage to the collagen network that supports the proteoglycan macromolecules due to an excess of type IX collagen fibers covalently bound to type II collagen fibers. Over time, type II collagen is completely reduced in synthesis, replaced by type I, which has lower strength and elasticity. The synthesis of proteoglycans is also altered, reducing their size, their ability to aggregate with hyaluronic acid (due to the cleavage of the binding protein), and the normal ratio of chondroitin sulfate to keratan sulfate (in the sense of increasing keratan sulfate) (19).

All these changes are accompanied by an increase in the permeability of the matrix and consequently in the water content, which leads to the softening of the cartilage and the decrease of its resistance to compression. The disorder is called chondromalacia and is irreversible. At the same time, by excessive hydration, the cartilage becomes more permeable to catabolic enzymes, which under

normal conditions of semi-hydrated proteoglycans diffuse only to a small extent. This closes a vicious circle, the chondrocytes, which are in direct contact with the extracellular matrix components, detecting changes in osmolarity and density at its level (20).

In the initial stages, some chondrocytes die, no longer being protected by a functional matrix, and the remaining viable ones suffer mitotic divisions, with the appearance of new chondrocyte clones. At their level, intense synthesis processes occur, both proteoglycans and collagen, and proteolytic enzymes (5-6 times more than normal). In the late stages, this synthesis collapses, and the cartilage becomes hypocellular. In many regions, hyaline cartilage is replaced by fibrocartilage, a type of cartilage rich in collagen I, with inferior mechanical qualities (19).

Abnormal chondrocyte synthesis is the result of their activation by cytokines, lipid mediators (prostaglandins), metabolic products of chondrocytes (such as nitric oxide), and extracellular matrix constituents themselves (fibronectin fragments). In turn, activated chondrocytes become able to synthesize some proteases and proinflammatory mediators. Type A (macrophage-like) synoviocytes that phagocytose cartilage fragments also contribute to this process, leading to synovial inflammation and the release into the joint cavity of mediators such as matrix-metal-proteinases (MMPs) and cytokines (21).

Thus, synovial macrophages perpetuate counter city activation and, in turn, contribute to the degradation of the extracellular matrix. Some cytokines such as IL-1 and TNF- $\alpha$ , but also nitric oxide, IL-17, IL-18 decrease the synthesis of matrix components, increase the synthesis of catabolic enzymes, decrease the proliferation of chondrocytes in a word and promote cartilage degradation. It has been found that in arthritic cartilage, chondrocytes have a higher number of receptors for IL-1 than normal, which makes them more susceptible to its action. In contrast, chondrocytes in the talus joints have low IL-1 receptors, which may explain the lower frequency of osteoarthritis at this level (19).

Other cytokines such as IGF-1 (insulin-like growth factor), TGF- $\beta$  (transforming growth factor) stimulate the synthesis of collagen fibers, proteoglycans and tissue inhibitors of matrix metalloproteinases (TIMP and inhibit the synthesis of MMP). In osteoarthritis, there was a decrease in the response of chondrocytes to these anabolic cytokines and a decrease in the concentration of TIME, which led to an imbalance between MMP and TIME (12). It can be considered that the balance between the synthesis and the formation of the components of the extracellular matrix is the basis of the degradation of the arthritic cartilage (22).

The changes in the subchondral bone are practically concomitant with those in the cartilage. The subchondral bone is repairing the joint damage, becoming very metabolically active. It has several processes: eburnation, i.e., subchondral osteosclerosis, hypervascularization, stimulation of osteoblasts with the formation of marginal osteophytes by bone hyperplasia, and neof ormation of cartilage. Bone hyperplasia is the starting point of the areas of cartilaginous metaplasia located at the edge of the subchondral bone or the insertion of the capsules and ligaments. However, the cartilage covering the newly formed bone contains type I collagen, which lacks the mechanical properties of type II. The underlying mechanism of osteophyte production is not fully elucidated (23).

Several hypotheses have been made in this regard: penetration of blood vessels in the basal layers

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