

REVIEW ARTICLE

Aetiological Factors of Osteoarthritis: A Review Update

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[Received on: 12 July, 2014; Reviewed on: 31 November, 2014; Accepted on: 31 December, 2014; Published on: 1 January 2015]

Abstract

Osteoarthritis (OA) is no longer considered 'degenerative' or 'wear and tear' arthritis; rather involves dynamic biomechanical, biochemical and cellular process. Indeed, the joint damage that occurs in OA is the result of active remodeling involving all the joint structures. Although articular cartilage is at the center of change, OA is viewed as a disease of the entire joint. Traditionally, OA has been viewed as an inevitable degenerative condition of the cartilage. It is currently viewed as a biomechanical and biochemical inflammatory disease of the entire joints. Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in the elderly, and the high rate of disability related to disease make it a leading cause of disability in the elderly. Because of the aging of Western populations and because obesity, a major risk factor, are increasing in prevalence, the occurrence of osteoarthritis is on the rise. In the United States, osteoarthritis prevalence will increase from 66–100% by the year 2020. OA affects certain joints, yet spares others. Commonly affected joints include the cervical and lumbosacral spine, hip, knee, and first metatarsal phalangeal joint (MTP). In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow, and ankle. [Journal of Current and Advance Medical Research 2015;2(1):18-23]

Keywords: Osteoarthritis, aetiology, risk factors

[Cite this article as: Islam MJ, Hossain MS, Amin MR, Ahmed M. Aetiological Factors of Osteoarthritis: A Review Update. J Curr Adv Med Res 2015;2(1):18-23]

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Conflict of Interest: There is no conflict of interest.

Contribution to authors: MJ, MSH & MRA prepared the manuscript. MRA & MA searched the articles.

Introduction

Osteoarthritis (OA) is the most common form of arthritis accounting for about 30% of general physician visits¹. OA is present by histologic or radiographic criteria; however, in nearly 80% of people by the age of 80 years only half of them have symptoms²⁻³. These are often variable and

intermittent. There is a modest correlation between the presence of symptoms and the severity of anatomic changes. All though variable in its presentation and course of OA often carries significant morbidity. In addition to the effects on the individual, the cost of OA to society is significant⁴, related to its high prevalence, the reduced ability of those affected

to perform both occupational and non-occupational activities, the occasional loss of a patient's ability to undertake self-care, and the related drain on health-care resources⁵.

Definition

It may be defined as a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins². It is usually classified as either primary (idiopathic) or secondary which is associated with a known condition. OA is joint failure, a disease in which all structures of the joint have undergone pathologic change, often in concert. The pathologic features of disease are hyaline articular cartilage loss, present in a focal and, initially, non-uniform manner³. This is accompanied by increasing thickness and sclerosis of the sub-chondral bony plate, by outgrowth of osteophytes at the joint margin, by stretching of the articular capsule, by mild synovitis in many affected joints, and by weakness of muscles bridging the joint⁴. In knees, meniscal degeneration is part of the disease.

Prevalence

The prevalence of OA correlates strikingly with age⁶. Regardless of how it is defined, OA is uncommon in adults under age 40 and highly prevalent in those over age 60⁷. It is also a disease that, at least in middle-aged and elderly persons, is much more common in women than in men, and sex differences in prevalence increase with age.

Global Considerations

Hip OA is rare in China and in immigrants from China to the United States⁸. However, OA in the knees, is at least as common, if not more so, in Chinese than in Caucasians from the United States, and knee OA represents a major cause of disability in China. Anatomic differences between Chinese and Caucasian hips may account for much of the difference in prevalence, with Caucasian hips having a higher prevalence of anatomic predispositions to the development

of OA. Persons from Africa, but not African Americans, may also have a very low rate of hip OA⁹.

Joint Protective Mechanisms and Their Failure

Joint protectors include: joint capsule and ligaments, muscle, sensory afferents, and underlying bone. Joint capsule and ligaments serve as joint protectors by providing a limit to excursion, thereby fixing the range of joint motion¹⁰. Synovial fluid reduces friction between articulating cartilage surfaces, thereby serving as a major protector against friction-induced cartilage wear. This lubrication function depends on the molecule *lubricin*, a mucinous glycoprotein secreted by synovial fibroblasts whose concentration diminishes after joint injury and in the face of synovial inflammation¹¹. The ligaments, along with overlying skin and tendons, contain mechanoreceptor sensory afferent nerves. These mechanoreceptors fire at different frequencies throughout a joint's range of motion, providing feedback by way of the spinal cord to muscles and tendons. As a consequence, these muscles and tendons can assume the right tension at appropriate points in joint excursion to act as optimal joint protectors, anticipating joint loading¹². Muscles and tendons that bridge the joint are key joint protectors. Their co-contractions at the appropriate time in joint movement provide the appropriate power and acceleration for the limb to accomplish its tasks. Focal stress across the joint is minimized by muscle contraction that decelerates the joint before impact and assures that when joint impact arrives, it is distributed broadly across the joint surface. The bone underneath the cartilage may also provide a shock-absorbing function, as it may give way subtly to an oncoming impulse load. Failure of these joint protectors increases the risk of joint injury and OA. For example, in animals, OA develops rapidly when a sensory nerve to the joint is sectioned and joint injury induced. Similarly, in humans, Charcot arthropathy, which is a severe and rapidly progressive OA, develops when minor joint injury occurs in the presence of posterior column peripheral neuropathy. Another example of joint

protector failure is rupture of ligaments, a well-known cause of the early development of OA¹³.

Cartilage and Its Role in Joint Failure

In addition to being a primary target tissue for disease, cartilage also functions as a joint protector. A thin rim of tissue at the ends of two opposing bones, cartilage is lubricated by synovial fluid to provide an almost frictionless surface across which these two bones move¹⁴. The compressible stiffness of cartilage compared to bone provides the joint with impact-absorbing capacity. Both the smooth frictionless surface and the compressive stiffness of cartilage serve as protective mechanisms preventing joint injury. Since the earliest changes of OA may occur in cartilage and abnormalities there can accelerate disease development, understanding the structure and physiology of cartilage is critical to an appreciation of disease pathogenesis. OA cartilage is characterized by gradual depletion of aggrecan, an unfurling of the tightly woven collagen matrix, and loss of type 2 collagen¹⁵.

Risk Factors

Joint vulnerability and joint loading are the two major factors contributing to the development of OA¹⁶. On the one hand, a vulnerable joint whose protectors are dysfunctional can develop OA with minimal levels of loading, perhaps even levels encountered during every day activities. On the other hand, in a young joint with competent protectors, a major acute injury or long-term overloading is necessary to precipitate disease. Risk factors for OA can be understood in terms of their effect either on joint vulnerability or on loading¹⁷.

Systemic Risk Factors

Age is the most potent risk factor for OA, with prevalence and incidence of disease rising dramatically with age. Radiographic evidence of OA is rare in individuals under age 40; however, in some joints, such as the hands, OA occurs in >50% of persons over age 70¹⁸. Aging increases joint vulnerability through several mechanisms. Whereas dynamic loading of joints stimulates cartilage matrix by chondrocytes in young

cartilage, aged cartilage is less responsive to these stimuli. Indeed, because of the poor responsiveness of older cartilage to such stimulation, cartilage transplant operations are far more challenging in older than in younger persons. Partly because of this failure to synthesize matrix with loading, cartilage thins with age, and thinner cartilage experiences higher shear stress at basal layers and is at greater risk of cartilage damage¹⁹. Aging also increases the likelihood of failure of major joint protectors. Muscles that bridge the joint become weaker with age and also respond less quickly to oncoming impulses. Sensory nerve input slows with age, retarding the feedback loop of mechanoreceptors to muscles and tendons related to their tension and position. Ligaments stretch with age, making them less able to absorb impulses. A combination of all of these factors works in concert to increase the vulnerability of older joints to OA. Older women are at high risk of OA in all joints, a risk that emerges as women reach their sixth decade; while hormone loss with menopause may contribute to this risk, there is little understanding of the vulnerability of older women's joints to OA²⁰.

Heritability and Genetics

OA is a highly heritable disease, but its heritability varies by joint. Fifty percent of the hand and hip OA in the community is attributable to inheritance, i.e., to disease present in other members of the family²¹. However, the heritable proportion of knee OA is at most 30%, with some studies suggesting no heritability at all²². Whereas many people with OA have disease in multiple joints, this "generalized OA" phenotype is rarely inherited and is more often a consequence of aging²³⁻²⁸. Emerging evidence suggests that persons with genetic mutations in proteins that regulate the transcription of major cartilage molecules are at high risk of OA. One gene implicated is *FRZB*, in which a mutation may put a woman at high risk of hip OA. *FRZB* is a gene for a Frizzled protein that antagonizes an extracellular Wnt ligand, and the Wnt signaling pathway plays a critical role in matrix synthesis and joint development²⁹.

Risk Factors in the Joint Environment

Some risk factors increase vulnerability of the joint through local effects on the joint environment³⁰. With changes in joint anatomy, for example, load across the joint is no longer distributed evenly across the joint surface, but rather shows an increase in focal stress. In the hip, three uncommon developmental abnormalities occurring in utero or childhood, congenital dysplasia, Legg-Perthes disease, and slipped femoral capital epiphysis, leave a child with distortions of hip joint anatomy that often lead to OA later in life³¹⁻³⁵. Girls are predominantly affected by acetabular dysplasia, a mild form of congenital dislocation, whereas the other abnormalities more often affect boys. Depending on the severity of the anatomic abnormalities, hip OA occurs either in young adulthood severe abnormalities or middle age mild abnormalities³⁶⁻³⁷. Major injuries to a joint also can produce anatomic abnormalities that leave the joint susceptible to OA. For example, a fracture through the joint surface often causes OA in joints in which the disease is otherwise rare such as the ankle and the wrist. Avascular necrosis can lead to collapse of dead bone at the articular surface, producing anatomic irregularities and subsequent OA³⁸⁻⁴⁰. Tears of ligaments that protect the joints, such as the anterior cruciate ligament in the knee and the labrum in the hip, can increase joint susceptibility and lead to premature OA. While meniscal tears may increase the risk of OA, meniscectomy operations, including selective ones, increase the risk of later disease, perhaps independent of the tear that led to the operation⁴¹. Even injuries that do not produce diagnosed joint injuries may increase risk of OA, perhaps because the structural injury was not detected at the time. For example, in the Framingham study subjects, men with a history of major knee injury, but no surgery, had a 3.5-fold increased risk for subsequent knee OA⁴². Another source of anatomic abnormality is mal-alignment across the joint. This factor has been best studied in the knee, which is the fulcrum of the longest lever arm in the body. Varus or bowlegged knees with OA are at exceedingly high risk of cartilage loss in the medial or inner compartment of the knee, whereas valgus (knock-kneed) mal-alignment predisposes to rapid cartilage loss in the lateral compartment.

Mal-alignment causes this effect by decreasing contact area during loading, increasing stress on a focal area or cartilage, which then breaks down. There is evidence that mal-alignment in the knee not only causes cartilage loss but leads to underlying bone damage, producing bone marrow lesions seen on MRI. While it is likely that the weakness in muscles bridging a joint increase the risk of OA in that joint, there is no definitive evidence in this regard. Patients with knee OA have impaired proprioception across their knees, and this may predispose them to further disease progression⁴³.

Loading Factors

Obesity: Three to six times body weight is exerted across the knee during single leg stance. Any increase in weight may be multiplied by this factor to reveal the excess force across the knee in overweight persons during walking⁴⁴. Obesity is a well-recognized and potent risk factor for the development of knee OA and, less so, for hip OA. Obesity precedes the development of disease and is not just a consequence of the inactivity present in those with disease. Obesity is a stronger risk factor for disease in women than in men, and in women, the relationship of weight to the risk of disease is linear, so that with each increase in weight, there is a commensurate increase in risk⁴⁵. Weight loss in women lowers the risk of developing symptomatic disease. Not only is obesity a risk factor for OA in weight-bearing joints, but obese persons have more severe symptoms from the disease. Obesity's effect on the development and progression of disease is mediated mostly through the increased loading in weight-bearing joints that occurs in overweight persons. However, a modest association of obesity with an increased risk of hand OA suggests that there may be a systemic metabolic factor circulating in obese persons that affects disease risk also.

Repeated Use of Joint: There are two categories of repetitive joint use, occupational use and leisure time physical activities⁴⁶. Workers performing repetitive tasks as part of their occupations for many years are at high risk of developing OA in the joints they use repeatedly. For example, farmers are at high risk for hip OA,

miners have high rates of OA in knees and spine, and shipyard and dockyard workers have a higher prevalence of disease in knees and fingers than do office workers⁴⁷. Even within a textile mill, women whose jobs required fine pincer grip [increasing the stress across the inter-phalangeal (IP) joints] had much more distal IP (DIP) joint OA than women of the same age whose jobs required repeated power grip, a motion that does not stress the DIP joints. Workers whose jobs require regular knee bending or lifting or carrying heavy loads have a high rate of knee OA. While exercise is a major element of the treatment of OA, certain types of exercise may paradoxically increase the risk of disease.

Conclusion

Despite the lack of strong, convincing, and reproducible evidence that intra-articular therapy significantly alters the short term outcome and even less so the progression of osteoarthritis, corticosteroid injection is one of the mainstays of the management of osteoarthritis, in particular, osteoarthritis of the knee.

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