RBO REVISTA BRASILEIRA DE ORTOPEDIA
www.rbo.org.br

Update Article

Is osteoarthritis a mechanical or inflammatory disease?☆,☆☆

*Márcia Uchôa de Rezende**, *Gustavo Constantino de Campos*

Institute of Orthopedics and Traumatology, Hospital das Clínicas, School of Medicine, University of São Paulo, São Paulo, SP, Brazil

ARTICLE INFO

Article history:
Received 14 March 2013
Accepted 19 March 2013

Keywords:
Osteoarthritis
Inflammation
Arthritis
Chronic disease
Mechanics

ABSTRACT

Traditionally considered "wear and tear" disease, the pathogenic mechanisms of osteoarthritis have not yet been elucidated. The increasing number of articles demonstrating the influence of inflammatory factors in the onset and progression of the disease currently raises great debate in the literature about the importance of each of the factors involved in the disease. Even the choice between the terms "Osteoarthritis" and "Osteoarthrosis" generates controversy, since the first term implies the presence of inflammation as the key generator of the disease, and the latter denotes a degenerative/mechanical causal factor. The aim of this revision article is to promote a debate on the influence of inflammatory factors and mechanical factors in the pathogenesis of OA.

A osteoartrite é uma doença mecânica ou inflamatória?

Palavras-chave:
Osteoartrite
Inflamação
Artrite
Doença crônica
Mecânica

RESUMO

Classicamente considerada uma doença de *wear and tear* (desgaste), a osteoartrite ainda não tem elucidados todos os seus mecanismos patogênicos. O crescente número de artigos que demonstram a influência dos fatores inflamatórios no surgimento e na evolução da doença suscita, atualmente, grande debate na literatura sobre a importância de cada um dos fatores envolvidos. Até mesmo a escolha dos termos osteoartrite e osteoartrose gera polêmica, uma vez que o primeiro implica a presença da inflamação como fator primordial gerador da doença e o último denota um fator causal degenerativo/mecânico. O objetivo deste artigo é promover um debate sobre a influência dos fatores inflamatórios e dos fatores mecânicos na patogênese da OA.

☆ Please cite this article as: de Rezende MU, de Campos GC. A osteoartrite é uma doença mecânica ou inflamatória? Rev Bras Ortop. 2013;48:471–474.

☆☆ Work performed at the Institute of Orthopedics and Traumatology, Faculty of Medicine, University of São Paulo, São Paulo, SP, Brazil.

* *Corresponding author.*
E-mail: murezende@uol.com.br (M.U. de Rezende).

2255-4971 http://dx.doi.org/10.1016/j.rboe.2013.12.002

Introduction

The concept that osteoarthritis (OA) is an inevitable consequence of aging, i.e. wear and tear on the joints due to use, is gradually being left behind. The term "degenerative joint disease", which is still greatly used, denotes the idea of futility and inevitability and does not express the true complexity of the problem. In view of the current knowledge, two sets of factors that seem to play a fundamental role in the development of OA have arisen: mechanical and inflammatory factors. However, there are divergent views in the literature regarding the importance to be given to each of these. The aim of this article was to promote a debate on the influence of inflammatory factors and mechanical factors on the pathogenesis of OA.

Taking the role of "devil's advocate", we firstly try to convince readers that OA is an inflammatory disease. We then present arguments in favor of treating it as a mechanical disease. We invite readers, before starting to read onwards, to choose just one of these theories. At the end, we believe that some readers will surprise themselves by changing their opinion after seeing the strong arguments on both sides.

Osteoarthritis is an inflammatory disease

The inflammatory process found in OA has been studied for several decades.[1,2] According to some recent studies,[3,4] OA behaves like an autoinflammatory disease, caused by responses mediated by chondrocytes and synoviocytes. The serum and synovial levels of inflammatory cytokines are higher in patients with OA.[5,6] There is much clinical evidence of the importance of inflammation in the pathogenesis of the disease, which even provides new potential therapeutic targets.[7]

Among the clinical signs seen in OA in any part of the body, there is an increase in joint volume, probably due to synovial effusion or thickening. This is an irrefutable sign of the presence of synovitis. There are increasing numbers of studies in the literature correlating synovitis with OA. In a search in PubMed using the terms *osteoarthritis* and *synovitis*, we found 1253 published papers with this association. Patients with OA frequently present episodes in which the condition becomes acute, known as flare-ups, which follow a course that includes joint effusion, pain when resting and/or morning stiffness.

Magnetic resonance imaging (MRI) with contrast and ultrasonography (US) are valid and efficient tools for studying synovitis.[8] Synovitis and joint effusion increase the risk of loss of cartilage in knees that initially do not have OA.[9] By means of arthroscopy, Ayral et al.[10] observed that the greater the degree of synovitis encountered was, the greater the chance of joint deterioration would be. In another study, great presence of inflamed tissue was observed in histological sections from osteoarthritic joints.[11]

In an experimental model for OA caused by means of collagenase-induced lesions,[12] the group in which the macrophages of the synovium were depleted before OA was induced did not present degradation. This signifies that macrophages have a fundamental role in the pathogenesis of OA and are not just a consequence of it. The stress mechanism itself often functions like a veritable cytokine.[13] Mechanical stress is picked up and interpreted by mechanical receptors, which then activate inflammatory cascades, exactly in the same way as occurs in activation caused by cytokines.[14]

Among patients with OA, a phenotype in which the disease accompanies metabolic disorders such as diabetes or obesity[15,16] clearly exists. Adipose tissue is capable of producing adipokines and other inflammatory mediators, which increase the levels of inflammatory activity throughout the body,[17] and even in osteoarthritic joints.[18] Obese patients present twice as much risk of presenting OA in their hands, which signifies that the greater incidence of OA in the knees and hips of obese individuals cannot be attributed only to their greater weight.[19]

Finally, it is known that aging increases the cellular response to inflammatory factors.[20] Cell senescence increases cytokine production and thus aging causes a state of chronic inflammation that is characterized as low-intensity, systemic and subclinical. To describe this state, Franceschi et al. introduced the term inflammaging,[21] as a combination between inflammation and aging.

Osteoarthritis is a mechanical disease

Saying that a disease is mechanical means that it is related to movement and physical forces, or is caused by these. This is precisely what leads to OA, i.e. increased physical force in localized areas of a joint. OA is a joint's pathophysiological response to a mechanical injury.[22] It represents an attempt by the joint to correct an abnormal mechanical stress and repair the injury resulting from this. Although some authors consider that increased levels of cytokines, free radicals and degradative enzymes in the joint are the cause of OA,[2–4,16] there is evidence indicating that in fact all inflammatory responses are the result of attempts to repair osteoarthritic joints.[23]

Among the causes that may lead to an abnormal increase in forces in localized areas of the joint, the following can be observed: (1) congenital or acquired abnormal anatomy, such as congenital misalignment or a meniscal or anterior cruciate ligament injury, which leads to increased stress even under physiological loads; (2) excessive loading, like in obese individuals; (3) a combination of factors, which is the commonest scenario. Moreover, it is not the misalignment that causes OA, but its effect of concentrating the intra-articular stress. It is not the estrogen deficiency or a genetic abnormality in itself, but the effects that stem from these alterations that cause the joint tissues to lose the ability to protect themselves adequately against loads that are often physiological.

Abnormal mechanics cause OA. Most animal models use focused load increases to cause OA (meniscal injury or resection of the ACL).[24] Wu et al.[25] caused OA in rabbits through inducing misalignment with an increase in varus moment. Animal models that do not cause injury (for example, using iodine acetate) do not resemble OA. There are no models with cytokines or inflammatory factors.

In humans, many studies have correlated meniscal injuries with OA.[26] Occasional meniscal injuries occur in 30–60% of individuals over the age of 50 years,[27] and their occurrence

increase the risk of developing OA tenfold.[28] Moisio et al.[29] clearly demonstrated that meniscal injuries precede cartilage losses, through finding that there was greater risk only of posterior cartilage loss in posterior meniscal tears, and greater risk of cartilage loss only in regions adjacent to meniscal body lesions. Surgery to remove meniscal injuries (even partial removal of menisci) increases the focal stress on the cartilage and causes high rates of OA.[26] Because of the high prevalence of meniscal injuries, both in young and in older individuals, these can be considered to be responsible for 40–50% of the cases of OA of the knees.

Misalignment causes OA.[30] Congenital hip dysplasia increases the risk of developing OA by 2.8-fold.[31] Varus alignment of the knee dysplasia increases the risk of developing OA in the medical compartment by around 3.5-fold.[30] Knees in varus alignment give rise to bone marrow injuries in the medial compartment, while valgus knees give rise to injuries in the lateral compartment.[32] An external adductor moment in the knee creates a vicious circle of varus, in that the greater the varus is, the greater the adductor moment will be. This increases the load in the medial compartment and leads to even greater varus, as well as releasing debris in the joint and in the bone marrow injuries. Interestingly, there is no inflammation in the bone marrow injuries found in cases of OA.[33] There is little edema, with much fibrosis and bone necrosis, and these characteristics show that the injuries are in fact fractures due to insufficiency. Once the abnormal mechanics have developed, they overwhelm all other factors. Therefore, the mechanics need to be treated, and the proof of this is the long-lasting success of treatment by means of varus-reducing osteotomy of the knee.[34] When this is correctly indicated, it can bring an improvement in symptoms that lasts for many years, in contrast with the transitory effect, without central action on the pathogenesis of OA, that is seen in treatments that focus on the inflammation, such as intra-articular injection of corticosteroids.[35]

In relation to risk factors for developing OA: (1) obesity certainly increases the load on the joint; (2) greater age probably leaves the knee more vulnerable to injury through a variety of factors, such as diminished muscle strength, for example; (3) occupational factors give rise to overload on specific joints, relating to the individual's occupation; and (4) the genetic influence for development of radiographic OA also relates to specific localities, i.e. families inherit OA of the knees, OA of the hands or OA of the hips. Thus, genetic inheritance of OA does not occur systematically, as had been thought. Generalized OA is not inherited but, rather, OS of a specific joint.[36] This may mean that, in reality, the inheritance comprises physical characteristics of a particular joint, which will lead to mechanical disorders that cause OA. None of these risk factors are related to inflammation. C-reactive protein (CRP), which is the most important of the inflammatory markers, does not present any correlation with OA.[37]

Final remarks

The international community is still absolutely divided regarding the exact mechanism of this disease. The answers to questions about the physiopathological mechanisms and factors involved in disease progression and treatment of OA unfortunately remain nebulous. This is a complex pathological condition resulting from interactions of a variety of causes and factors. Considering the problem to be purely mechanical or purely inflammatory seems to be an attempt to simplify something that is not simple.

The fundamental concept is that this is a failure of an entire joint, i.e. a complete organ that is composed not only of cartilage but also of various tissues such as the synovium, subchondral bone, capsule, menisci, muscles and tendons. The therapy should therefore be holistic and encompass a wide diversity of aspects of the disease. There is still a need for greater amounts of information than what is currently available, for any attempt to reach a definitive conclusion on this matter.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Dieppe P. Inflammation in osteoarthritis. Rheumatol Rehabil. 1978; Suppl.:59–63.
2. Pincus T. Clinical evidence for osteoarthritis as an inflammatory disease. Curr Rheumatol Rep. 2001;3(6):524–34.
3. Konttinen YT, Sillat T, Barreto G, Ainola M, Nordstrom DC. Osteoarthritis as an autoinflammatory disease caused by chondrocyte-mediated inflammatory responses. Arthritis Rheum. 2012;64(3):613–6.
4. Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis, and inflammation. Rheumatology (Oxford). 2005;44(1):7–16.
5. Sohn DH, Sokolove J, Sharpe O, Erhart JC, Chandra PE, Lahey LJ, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. Arthritis Res Ther. 2012;14(1):R7.
6. Pearle AD, Scanzello CR, George S, Mandl LA, DiCarlo EF, Peterson M, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. Osteoarthritis Cartilage. 2007;15(5):516–23.
7. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum. 2001;44(6):1237–47.
8. Guermazi A, Roemer FW, Hayashi D. Imaging of osteoarthritis: update from a radiological perspective. Curr Opin Rheumatol. 2011;23(5):484–91.
9. Roemer FW, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis. 2011;70(10):1804–9.
10. Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis—results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage. 2005;13(5):361–7.
11. Young L, Katrib A, Cuello C, Vollmer-Conna U, Bertouch JV, Roberts-Thomson PJ, et al. Effects of intraarticular glucocorticoids on macrophage infiltration and mediators of joint damage in osteoarthritis synovial membranes: findings

in a double-blind, placebo-controlled study. Arthritis Rheum. 2001;44(2):343–50.
12. Blom AB, van Lent PL, Libregts S, Holthuysen AE, van der Kraan PM, van Rooijen N, et al. Crucial role of macrophages in matrix metalloproteinase-mediated cartilage destruction during experimental osteoarthritis: involvement of matrix metalloproteinase 3. Arthritis Rheum. 2007;56(1):147–57.
13. Kawakita K, Nishiyama T, Fujishiro T, Hayashi S, Kanzaki N, Hashimoto S, et al. Akt phosphorylation in human chondrocytes is regulated by p53R2 in response to mechanical stress. Osteoarthritis Cartilage. 2012;20(12):1603–9.
14. Piscoya JL, Fermor B, Kraus VB, Stabler TV, Guilak F. The influence of mechanical compression on the induction of osteoarthritis-related biomarkers in articular cartilage explants. Osteoarthritis Cartilage. 2005;13(12):1092–9.
15. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol. 2012;8(12):729–37.
16. Berenbaum F. Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. Postgrad Med J. 2012;88(1038):240–2.
17. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med. 2012;18(3):363–74.
18. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. Curr Opin Rheumatol. 2010;22(5):533–7.
19. Yusuf E. Metabolic factors in osteoarthritis: obese people do not walk on their hands. Arthritis Res Ther. 2012;14(4):123.
20. Forsyth CB, Cole A, Murphy G, Bienias JL, Im HJ, Loeser Jr RF. Increased matrix metalloproteinase-13 production with aging by human articular chondrocytes in response to catabolic stimuli. J Gerontol A Biol Sci Med Sci. 2005;60(9): 1118–24.
21. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflammaging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.
22. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. Med Clin North Am. 2009;93(1):1–24.
23. Brandt KD, Dieppe P, Radin EL. Commentary: is it useful to subset “primary” osteoarthritis? A critique based on evidence regarding the etiopathogenesis of osteoarthritis. Semin Arthritis Rheum. 2009;39(2):81–95.
24. Papaioannou N, Krallis N, Triantafillopoulos I, Khaldi L, Dontas I, Lyritis G. Optimal timing of research after anterior cruciate ligament resection in rabbits. Contemp Top Lab Anim Sci. 2004;43(6):22–7.
25. Wu DD, Burr DB, Boyd RD, Radin EL. Bone and cartilage changes following experimental varus or valgus tibial angulation. J Orthop Res. 1990;8(4):572–85.
26. Papalia R, Del Buono A, Osti L, Denaro V, Maffulli N. Meniscectomy as a risk factor for knee osteoarthritis: a systematic review. Br Med Bull. 2011;99:89–106.
27. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med. 2008;359(11):1108–15.
28. Englund M, Guermazi A, Roemer FW, Aliabadi P, Yang M, Lewis CE, et al. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: the Multicenter Osteoarthritis Study. Arthritis Rheum. 2009;60(3):831–9.
29. Moisio K, Chang A, Eckstein F, Chmiel JS, Wirth W, Almagor O, et al. Varus-valgus alignment: reduced risk of subsequent cartilage loss in the less loaded compartment. Arthritis Rheum. 2011;63(4):1002–9.
30. Hayashi D, Englund M, Roemer FW, Niu J, Sharma L, Felson DT, et al. Knee malalignment is associated with an increased risk for incident and enlarging bone marrow lesions in the more loaded compartments: the MOST study. Osteoarthritis Cartilage. 2012;20(11):1227–33.
31. Lane NE, Lin P, Christiansen L, Gore LR, Williams EN, Hochberg MC, et al. Association of mild acetabular dysplasia with an increased risk of incident hip osteoarthritis in elderly white women: the study of osteoporotic fractures. Arthritis Rheum. 2000;43(2):400–4.
32. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med. 2003; 139 (5 Pt 1):330–6.
33. Taljanovic MS, Graham AR, Benjamin JB, Gmitro AF, Krupinski EA, Schwartz SA, et al. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. Skeletal Radiol. 2008;37(5):423–31.
34. Brouwer RW, Jakma TS, Bierma-Zeinstra SM, Verhagen AP, Verhaar J. Osteotomy for treating knee osteoarthritis. Cochrane Database Syst Rev. 2005;1:CD190040.
35. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006;2:CD280053.
36. MacGregor AJ, Li Q, Spector TD, Williams FM. The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee. Rheumatology (Oxford). 2009;48(3):277–80.
37. Vlad SC, Neogi T, Aliabadi P, Fontes JD, Felson DT. No association between markers of inflammation and osteoarthritis of the hands and knees. J Rheumatol. 2011;38(8):1665–70.