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Osteoarthritis as a disease of mechanics

David T. Felson
Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA and Arthritis Research UK Epidemiology Unit, University of Manchester Manchester, UK

Abstract

Mechanics means relating to or caused by movement or physical forces. In this paper, I shall contend that OA is almost always caused by increased physical forces causing damage to a joint. While examples of joint injury causing osteoarthritis are numerous, I shall contend that most or almost all osteoarthritis is caused in part by mechanically induced injury to joint tissues. Further, once joint pathology has developed, as is the case for almost all clinical osteoarthritis, pathomechanics overwhelms all other factors in causing disease progression. Treatments which correct the pathomechanics have long lasting favorable effects on pain and joint function compared with treatments that suppress inflammation which have only temporary effects. I shall lastly contend that the mechanically induced joint injury leads to variable inflammatory responses but that the role of this inflammation in worsening structural damage in an already osteoarthritic joint has not yet been proven.

Keywords

osteoarthritis; biomechanics; inflammation

Introduction

The Oxford English dictionary defines mechanics as relating to or caused by movement or physical forces. I shall contend that OA is almost always caused by increased physical forces causing damage to a joint. The hypothesis that I will entertain is that OA is caused by increased forces across a local area of a joint either from *a)* abnormal anatomy (congenital or acquired) leading to increased focal stress with the overall load across the joint being normal; or *b)* excess overall load either acutely or chronically such as might occur with an injury during sports or with obesity chronically or *c)* a combination of anatomy and excess load. The latter might occur in a situation where an obese person has a slightly deformed joint, perhaps on a congenital basis, and develops OA in that joint.

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Address correspondence to Dr. Felson at X200, 650 Albany Street, Boston University School of Medicine, Boston, MA 02118; dfelson@bu.edu.

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This paper is derived from a debate at the 2012 OARSI meetings in Barcelona on whether osteoarthritis is a disease of mechanics or an inflammatory disease.

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Proving abnormal stresses across the joint causes OA is not a challenging proposition. Animal models of OA almost all rely on joint injury to induce disease. Further, it has been known for at least 60 years[1] that meniscal tears and meniscectomies done after tears lead to an extremely high risk of OA, suggesting that abnormal focally increased forces across the knee certainly cause OA. I will attempt to prove a more challenging hypothesis, that abnormal mechanical forces cause most or even all OA. I note further that causes do not work alone to cause disease. Diseases are often the result of an interplay between causes, a fact evident in OA. A major injury (one cause) when combined with older age at the time of injury[2] is more likely to produce OA than a major injury alone. Further, overweight young persons have only a modest risk of OA but older, overweight persons have a very high risk of knee OA. And the proportion of those with knee OA increases further when the person is not only obese and older but also female. In considering causes of OA, I will contend that mechanical forces play a role in almost all OA but that they do not necessarily act by themselves in causing disease.

Causation is difficult to prove for complex noninfectious human diseases. Generally, proving causation requires an intervention in which a putative causal agent is added or removed and the organism followed to see if they develop disease. Ideally, animal models provide this opportunity, but in osteoarthritis, animal models test causal agents by inducing injury in a normal non-diseased joint and evaluate whether a causal or preventive agent prevents joint damage in the face of this injury. This is not a model for most human osteoarthritis in which symptoms occur and patients present for treatment only after considerable joint pathology exists. It is ethically impossible to test many causal agents in human osteoarthritis, so this review will infer causation when there has been a consistently found and temporally appropriate relationship between a risk factor (e.g. meniscal tear) and later onset of disease (e.g. osteoarthritis) and when that relationship has biological plausibility (for details of criteria for causality, see Chapter 2 in Rothman and Greenland[3].

To demonstrate the pivotal role of abnormal mechanics in causing OA, I shall make three arguments. First, abnormal mechanics cause OA both in animals and humans. Second, once OA has developed, abnormal mechanics overwhelms all other factors in terms of leading to disease worsening. And third, inflammation in OA is mostly a consequence of abnormal mechanics and is almost never primary. This is not a systematic review but rather draws from selected research findings to make certain points. Further, except when specified, it focuses on structural disease as opposed to pain. Pain is often affected by psychosocial and other factors, making it harder to determine its causes.

Abnormal mechanics causes OA

Among the best examples that abnormal mechanics can cause OA is the widespread use of surgically induced injuries that cause OA in animal models of disease. These include ACL transection and meniscal injury models in numerous strains of animals. An intriguing example demonstrating the effect of focal areas of overload was produced by David Wu and colleagues many years ago[4] in which they induced cartilage degradation in rabbits by creating 10° varus malalignment and not entering the knee jo int. These knees were then compared to the contralateral unoperated knee and for each of the rabbits, histologic changes of cartilage degradation were far greater in the operated than in the unoperated limbs, suggesting that abnormal loading caused disease.

In humans there are many examples of major joint injuries or abnormally shaped joints producing high levels of focal stress across the joint causing OA. First it has been known for at least 60 years[1] that meniscal tears and meniscal removal lead to increased focal stress across the joint and subsequently high rates of OA. Menisci serve as washers to increase

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stability within the joint and to distribute load so that when the meniscus is intact, focal stress is kept at low levels[5]. When menisci are removed (or even partially removed), injury to areas of the joint where the meniscus was removed is far more likely with one large follow-up study estimating that half the knees that underwent meniscectomy during young adulthood had evidence of radiographic osteoarthritis 21 years later (vs. 7% in knees without meniscectomy) (Odds Ratio for OA development 14.0 (95% CI 3.5, 121.2)[6]). In fact, in joints where the meniscus has been removed and most of it is gone, the only preserved area of cartilage is the small area of the joint where the meniscus remains[7]. Tears of the anterior cruciate ligament are also associated with high rates of OA for reasons that are likely to do with increased compressive stress across the medial compartment of the knee where most of the disease in ACL tear patients occurs[8,9]. ACL tears are especially likely to lead to OA when accompanied by meniscal tears[8].

While it has long been known that traumatic major tears of the meniscus in young athletes lead to high rates of later knee OA, recent evidence suggests that meniscal tears occurring in middle aged and older persons may be a common precipitant of disease. Englund et al[10] showed in a population-based sample recruited without reference to knee pain that 30–60% of adults aged 50 and over had incidental meniscal tears. Many of these persons did not recall any injury to their knees. Following those with incidental meniscal tears in a later cohort study, Englund et al then demonstrated that persons with tears and no other cartilage damage were at marked increased risk of developing cartilage damage and subsequent radiographic OA[11]. In fact, among knees with only incidental meniscal tears, the risk of developing OA within 30 months was increased 10-fold compared to those without such tears[12]. Chang et al.[13] demonstrated that meniscal tears did not just precede OA but they increased the risk of cartilage loss adjacent to the meniscal tear, not just cartilage loss throughout the joint. A posterior medial meniscal tear increased the risk of only posterior cartilage loss, and a tear in the body of the medial meniscus increased the risk of only adjacent cartilage loss, suggesting that meniscal tear per se increased focal stress on the underlying cartilage in that small limited region.

Meniscal tears therefore appear to be a consequence of major trauma at a young age often as an injury during sports participation but occur with minor trauma in older years. Regardless of when those tears occur, they appear to markedly increase the risk of OA by increasing focal loading or stress across adjacent areas of cartilage, leading to cartilage breakdown and subsequent changes of OA. These tears are common and confer an extremely high risk of later OA. Given the high prevalence and risk conferred, meniscal tears may account for as much as 40–50% of human knee OA. Meniscal tears serve as one of the major pieces of evidence that abnormal mechanics causes OA.

Meniscal tears are not the only common risk factor of mechanical basis that leads to high rates of knee OA. In recent work, Sharma et al.[14], working with data from the MOST study, showed that knees without any cartilage damage that were from varus limbs were at high risk of subsequent cartilage loss. After adjusting for age, gender, body mass index and lateral laxity, varus knees had 3.5-fold increased odds of development of cartilage loss compared to knees without any varus deformity. This suggests, like the rabbit studies from Wu and colleagues, that malalignment causes increased stress across a focal area of the joint leading to damage there and subsequent disease. Indeed, some incidence studies looking at malalignment have shown that varus malalignment is associated not just with cartilage loss but with high rates of radiographic OA and even symptomatic disease later[15,16].

If mechanical causes of knee OA are common, hip OA may serve as the best example whereby mechanical load or abnormal stresses cause almost all disease. There are at least two anatomic abnormalities that occur often in childhood that predispose to high rates of

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OA. On the one hand, dysplasia which can occur congenitally puts increased focal stress on a small area of the acetabulum which provides insufficient coverage for the femur. Congenital dysplasia when severe is recognized often in infancy and corrected. When modest, it is uncorrected and increases markedly the risk of hip OA occurring at a young adult age. Further, Lane and colleagues[17] have shown that mild dysplasia even present in adulthood increases the risk of later life hip OA, a finding corroborated by other longitudinal studies.

A potentially more prevalent cause of increased focal stress across the hip is femoroacetabular impingement (FAI). FAI consists of a variety of anatomic abnormalities, but the most common are cam and pincer deformities, which appear to be highly prevalent in young adults[18]. At work presented at the 2012 OARSI meetings, groups in the Netherlands[19] and investigators from the Chingford Study[20,21] convincingly showed that femoroacetabular impingement seen on x-ray in these studies markedly increases the risk of later clinical hip OA, of radiographic disease, and even of the likelihood of hip replacement. Thus, evidence is quickly accumulating that anatomic abnormalities associated with femoroacetabular impingement are major risk factors predisposing to later-life hip OA, suggesting once again that mechanical abnormalities overwhelm others as causes of this disease.

If there is remaining doubt, one excellent example pointing to the importance of hip shape abnormalities is our understanding of why Chinese populations are only rarely affected by hip OA. In the Beijing OA Study, a population-based study of older adults from Beijing[22], only one case of symptomatic hip OA was found among 1800 older subjects drawn from the city of Beijing. Over 25 such cases would be expected if rates in Beijing were similar to rates in Western populations. In a study of non-diseased hips drawn from Beijing and from Western populations in which morphometry was assessed, Dudda et al.[23] reported that anatomical changes suggesting femoroacetabular impingement were far more common in Caucasian than in Chinese populations, the latter of which tended to have purely spherical femoral heads. Surprisingly, evidence of mild dysplasia was, if anything, more common among Chinese. Further, Chinese populations actually had higher rates of knee OA than did Western populations, suggesting that the low rate of OA in the hips was not a function of low generalized OA rates.

Knee and hip OA are not unique in being strongly related to injury and mechanics. In joints rarely affected by OA such as the ankle, major injury accounts for almost all cases of disease[24].

While it is obvious that some mechanical abnormalities such as ACL and meniscal tears cause a subset of knee OA, the bigger question is whether mechanical factors account for almost all knee OA as they appear to do for hip OA. Major risk factors for knee OA according to recent reviews include: older age, female gender, obesity, knee injury and occupational overuse[25,26]. Other than older age and female gender which increase the vulnerability of structures within the knee to injury, all of the factors that have been identified consistently represent types for mechanical overload. For knees, obesity represents chronic excess loading, whereas knee injury produces focal increased stress. The risk of OA in joints in which there has been stereotyped repetitive use patterns typical of occupations has been well documented and represents another type of chronic excess load. For example, cotton workers have a high rate of OA in their finger joints[25]. Miners have a high rate in their knees and spines, jackhammer operators experience excess rates of OA in joints that are very rarely affected by disease such as elbows, wrists and metacarpalphalangeal joints. Farmers get high rates of OA in their hips and knees.

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One factor that is not on the list of causes of knee or other OA is inflammation. Even though isolated studies have reported that elevated C-Reactive Protein (CRP) levels are associated with certain phenotypes of OA, large-scale studies evaluating this question have been consistently negative. For example, data from the Framingham Study, Health ABC, and Johnston County have all shown that elevated CRP levels are not associated with OA in any joint[27,28].

Another piece of evidence that mechanical forces induce all or almost all human OA consists of data from genetic studies. While the heritability of OA is moderate, much of it is joint-specific. As documented by MacGregor and colleagues[29], the genetic influence on radiographic OA is site-specific at hand, hip and knee, a finding that has been confirmed also in the Framingham Study[30]. Specifically, MacGregor et al. reported that once environmental correlations were removed from family data on OA at multiple joints, the correlations between the occurrence of OA in the distal interphalangeal joints of the hands and that of the knee was actually a r = −.008 suggesting a trivial but inverse correlation of knee OA with distal interphalangeal joint (DIP) OA. The relation of DIP joint OA with hip OA was remarkably small (r = .036) and DIP OA was not even strongly associated from a genetics perspective with OA in the adjacent thumb base. Thus, even the genetics of OA suggest that there is no systemic predisposition but rather that the genetics of OA as a joint-specific disorder is likely due to inherited joint shape predisposing to aberrantly elevated stresses across local areas of joint leading to cartilage breakdown and other changes of OA.

Once OA has developed, pathomechanics overwhelms all other factors

In the knee the onset of OA is accompanied by the development of either varus or valgus malalignment (depending on whether the disease develops predominantly in the medial or lateral compartment respectively). Malalignment causes a vicious circle of joint damage (see Figure 1). The narrowed area in a malaligned joint is subjected to increased load bearing that leads to increased cartilage damage, releasing debris into the joint space which then gets ingested by synovium, which becomes secondarily inflamed, secreting excess fluid. In addition to cartilage being damaged, the underlying bone undergoes remodeling and damage. The bone cortical envelope may remodel, creating more malalignment. The loss of cartilage, the damage to the meniscus which often becomes extruded, and the change in bone shape create an environment where malalignment, if anything, gets more severe. This then leads to more focal stress across the narrowed area of the joint, leading to more damage. A vicious cycle ensues.

Bone marrow lesions are present underneath the cortical surface of malaligned joints. If there is varus malalignment, there is an increasing risk for medial bone marrow lesions both in the tibia and the femur. If there is valgus malalignment, bone marrow lesions tend to occur on the lateral side of the joint[31]. Bone marrow lesions show evidence of bone trauma with healing microfractures, adjacent osteoblasts and osteoclasts, and bone marrow necrosis. There are reversal lines in bone, suggesting microcracks[32]. Ironically, even though on MRI the lesions would appear to contain water, there is little edema on histology in these lesions and there are no inflammatory infiltrates. Bone marrow lesions are the structural equivalent of malalignment in the knee.

Before developing OA, knees are mostly neutrally aligned with normal mechanical axis ranging from −1 (varus) to +1 (valgus). When knees develop OA they become more malaligned by a median of 1.7° either varus or valgus (per unpublished data from MOST Study in which there are repeated long limb films on subjects). Among knees with radiographic tibiofemoral OA, only 18% of osteoarthritic knees are neutral with 82% of them being clinically malaligned[33]. There are more knees that are varus than valgus

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malaligned, and up to 20% of OA knees have severe varus malalignment of >7°. The 82% figure of the prevalence of malalignment in osteoarthritic knees does not count the substantial number of knees with patellofemoral malalignment, nor does this figure take into account the possibility of dynamic malalignment (during walking) occurring in knees which look neutral statically. Therefore, it is probable that roughly 80–90% of knees with radiographic OA have substantial degrees of tibiofemoral and/or patellofemoral malalignment which predispose these knees to increased focal load and further damage. If we assume that 82% of osteoarthritic knees have tibiofemoral malalignment and also that there is an increased risk of progression according to studies by Sharma et al[34] and Felson et al.[31], then the proportion of tibiofemoral disease progression due to malalignment is roughly 60%. This does not necessarily include dynamic malalignment when walking which has also been shown to markedly increase the risk of disease progression[35]. It also does not count other causes of progression that are also mechanically driven such as meniscal tears or extrusion or possible sources of dynamic laxity in the knee. Thus, the preponderance of progression of extant knee OA is mechanically driven.

One way of evaluating whether mechanical factors or inflammatory factors are more important in determining the course of OA is to evaluate the effects of correcting each of these abnormalities. High tibial osteotomy (HTO) surgery corrects malalignment without entering the knee. In a classic study of the effects of high tibial osteotomy, Prodromos et al[36] reported that of patients who underwent HTOs and who had reduction in their dynamic varus momen[37]t, there were no clinical failures based on Hospital for Special Surgery rating scale[38] over an average of 3.2 years follow-up. In contrast, among patients who underwent this surgery but whose varus moment was not reduced, only 50% had satisfactory results.

When we compared this correction of mechanical abnormalities with correction of the inflammation that occurs in OA, we find stark differences. Among the most potent anti-inflammatories available for treatment are corticosteroids which can be injected intra-articularly. In studies evaluating the efficacy of intra-articular steroid vs. placebo injection, there has been a consistent finding[39] that steroids work better than placebo but that this effect is not durable. The efficacy of steroids exceeds placebo for 1–2 weeks after the injection and then wears off. Admittedly steroids are not supposed to be a permanent cure, but a substantial minority of patients do not have even temporary responses to intraarticular steroids, suggesting that at least in them, inflammation plays at best a minor role in their symptoms. In terms of structural disease, Myers et al[37] showed that continuous steroid treatment of dogs with induced OA did not have any effect on long term structural changes in their OA. Therefore, treatment to correct inflammation vs. mechanics provides us with stark information about what the real cause of OA is. Correcting abnormal mechanics corrects and alleviates the problem for many years. Correcting the increased inflammation has only a transient effect on disease because inflammation is not central to OA pathogenesis.

Inflammation in osteoarthritis is mostly a consequence of pathomechanics

Many joints with OA have evidence of inflammation with synovitis or with inflammatory cytokines present in the cartilage matrix; generally, some inflammation on a microscopic level is present. The hypothesized role of inflammation is shown in Figure 2. Generally, joint injury produces injury into the joint and consequent pathomechanics. That injury can then lead to release of cytokines and even infiltration of inflammatory cells within the synovium. The joint injury may work on its own to cause joint damage without any involvement from the inflammation that has been produced or the inflammation can accelerate or magnify the injury that is produced by pathomechanics.

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Evidence from multiple clinical studies already shows considerable evidence that injury to the joint can lead to secondary inflammation. For example, in a magnetic resonance imaging scan[40] in a paper on the co-occurrence of meniscal tears and synovitis (Figure 3), Roemer et al showed even without any other lesions in the knee, that the presence of a meniscal tear was associated with isolated synovitis suggesting that the tear brought on that secondary synovitis. As Higuchi and colleagues noted[41], most persons after an ACL tear develop high levels of interleukin 6 in their synovial fluids, levels far higher than are seen in normals.

The issue with respect to inflammation is not whether inflammation is present within osteoarthritic joints. It is to a variable extent. Rather the issue is how much and whether inflammation contributes to the joint damage experienced as a consequence of pathomechanics. While in animal models and in vitro studies, inflammatory cytokines accelerate the degradation of cartilage when it is subjected to damage from mechanical forces, it is not clear whether and how much these inflammatory mediators affect the human osteoarthritic joint or whether they play a major role in joint damage. Animal models of OA replicate mostly posttraumatic OA, occurring on the substrate of a normal joint. This is true even of the remarkable MRL/MpJ mice that despite intraarticular fractures do not get OA[42]. Osteoarthritic joints in humans are joints that, as noted above, have already sustained damage and where pathomechanics predominate. The role of inflammation in contributing to the further destruction of the human osteoarthritic joint is likely, but has not been proven. The strikingly focal nature of damage in OA and our ability to explain this focal injury by invoking mechanical explanations without any inflammation suggests that abnormal mechanics is still the basis for human OA.

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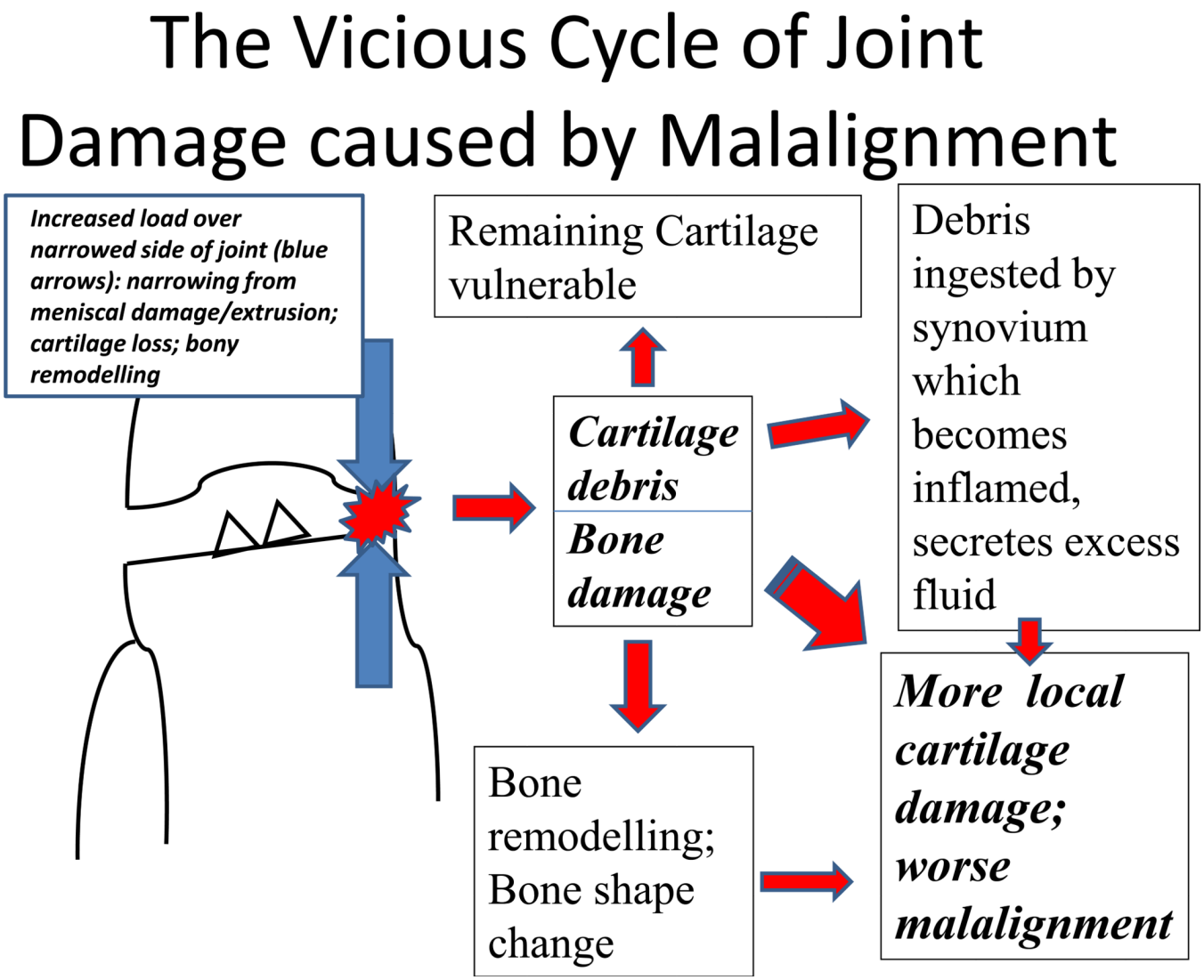

Figure 1.

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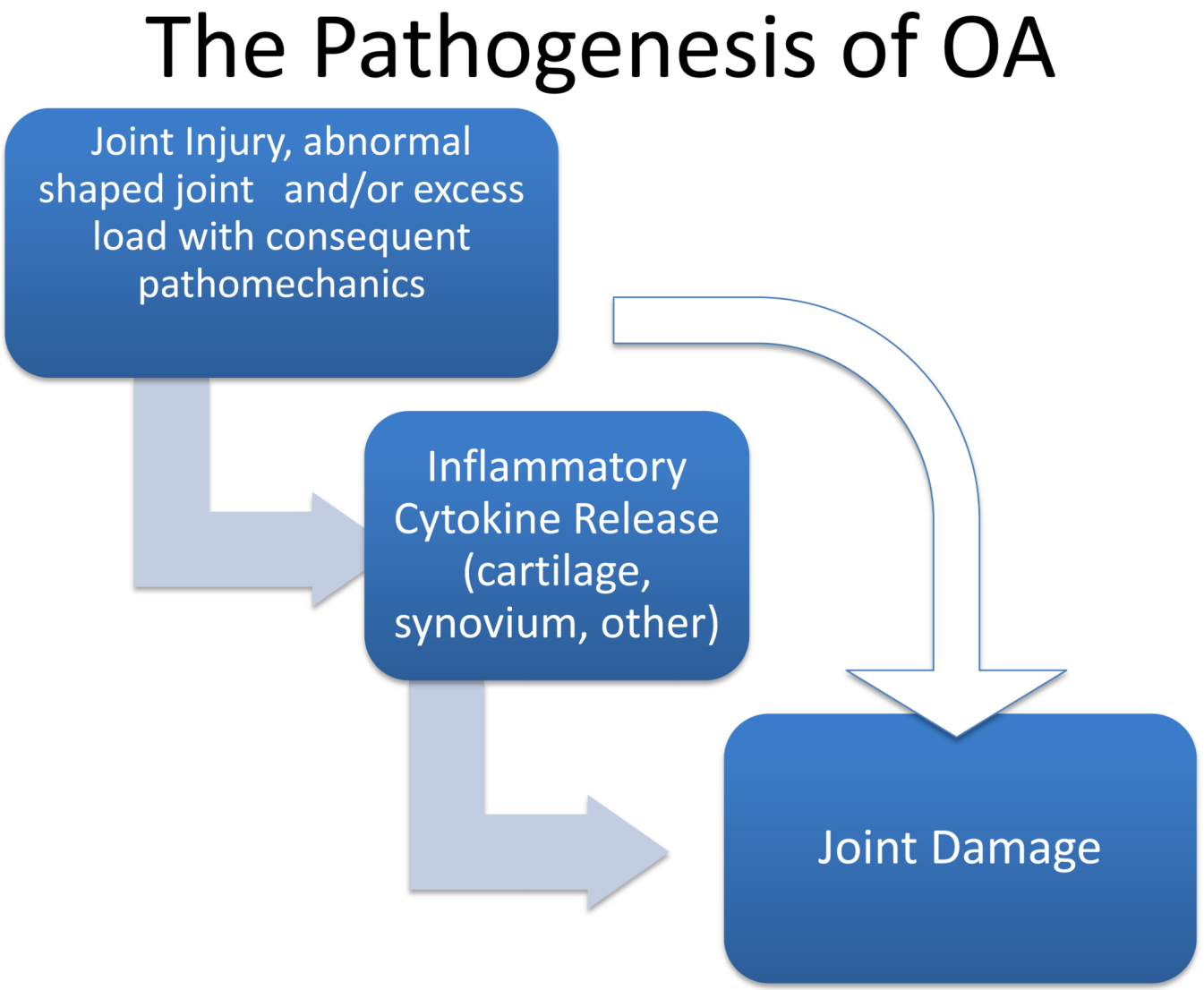

Figure 2.

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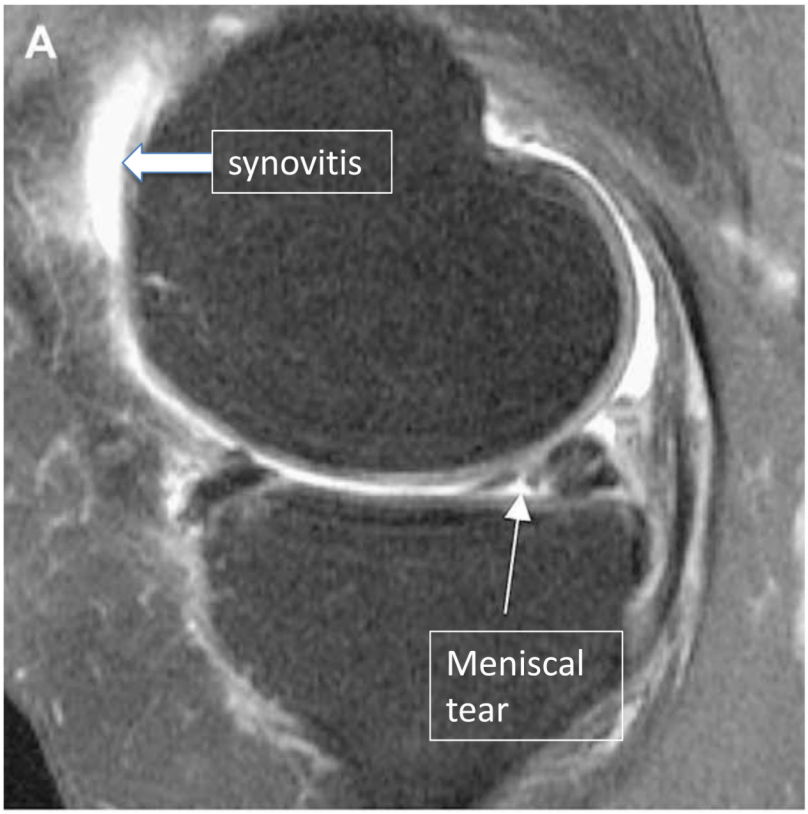
Meniscal tear and inflammation? Isolated meniscal tear is associated with synovitis*



*From Roemer et al, OA Cart, 2009

Figure 3.