What is New in the Treatment of Osteoarthritis Pain?
Part I: Current State of Knowledge of the Pathophysiology of Osteoarthritis

An estimated 49.9 million Americans have been diagnosed with some form of arthritis—approximately 1 in 5 adults.\(^1\) This number is expected to increase substantially, not only because of our rapidly aging population, but also because of the increasing prevalence of obesity, which increases the risk for arthritis. By 2030, 67 million Americans are expected to have arthritis, with approximately 25 million suffering from arthritis associated with disability.\(^2,3\) The implications of this looming growth in arthritis for the health care system are alarming. The Centers for Disease Control and Prevention (CDC) estimates the annual economic burden for all forms of arthritis at $128 billion, with $81 billion in direct medical costs and $47 billion in lost income (based on a 2003 Medical Expenditures Panel Survey).\(^3\) Given the expected growth in disease prevalence over the coming decades, the costs to the health care system are likely to be enormous.\(^4\)

Osteoarthritis (OA) is by far the most common form of arthritis; affecting 27 million Americans, most of them older than 45 years.\(^5,6\) The lifetime risk for symptomatic hip OA is 25.3% and for symptomatic knee osteoarthritis, 44.7%.\(^7,8\) Thus, it is not surprising that this disease is a leading cause of disability and a major driver of arthritis related health care costs.\(^9\) The mean total annual adjusted direct medical care costs for OA in 2007 were $18,435 per patient—more than double the costs for matched controls without OA ($7,494).\(^10\) By 2015, aggregate costs for total hip or knee replacement in OA alone are expected to exceed $65 billion.\(^11\)

With the exception of joint replacement, nothing currently approaches a “cure” for OA.\(^4\) Only palliative treatment is available. Nor is there any FDA approved biomarker for OA, limiting the ability to detect preradiographic disease: the point at which there might be opportunity to intervene before irreparable joint damage occurs. Ongoing research, however, is changing our understanding of the underlying pathophysiology of OA and is offering hope that we may see the advent of treatments that affect the disease process itself.

Disease Characteristics and Risk Factors

The classic radiographic features of OA include osteophyte formation, subchondral bone sclerosis, and joint space narrowing—while is a surrogate for both cartilage loss, meniscal degeneration and extrusion.\(^12\) These changes may or may not be accompanied by symptoms.\(^6\) Although many patients are diagnosed when symptoms occur and radiographic evidence is documented, by the time such changes are observed, patients typically have late-stage disease.\(^13\)
Osteoarthritis typically affects certain joints such as the hips, hands, knees, lower back, and neck. However, injury can cause OA in any joint and location of disease can often be a clue to its cause. For example, OA in the medial compartment of the knee is likely to be idiopathic in origin while disease in the lateral compartment is likely to be caused by trauma. (Figure 1)

Figure 1. Knee on the Left Shows Predominant Damage to the Medial Compartment and Is Likely to Be Idiopathic in Origin, While the Knee on the Right Shows Damage to the Lateral Compartment and Is Likely to Be Traumatic in Origin


Risk factors provide some clues as to what may underlie the disease process. Osteoarthritis is often thought of as a disease of the elderly, and while age is certainly an important risk factor, symptoms typically begin after age 40 and they may occur even earlier. Involvement in sports also has been considered a risk factor, but evidence indicates that sports related injuries and not the sport itself increase the
risk of developing OA. Joint injury is the most common risk factor for OA in young adults. Among young women who sustained an anterior cruciate ligament (ACL) injury while playing soccer, 51% had radiographic changes after 12 years. Among young men with ACL injuries from soccer, 41% had OA in the knee after 14 years. Female sex also predisposes an individual to OA. In an epidemiologic study, men had a lifetime risk of developing knee OA of 39.8% compared with 46.8% for women. As noted previously, there is a clear relationship between weight and the development of arthritis. Body mass index (BMI) appears to play a significant role in the development of the disease as well, particularly in the knee joint. In that same epidemiologic study, individuals who had a normal weight across their life course had the lowest lifetime risk (29.2%) of developing OA of the knee. In contrast, those who reported a normal weight at age 18 years but were overweight or obese later in life had the highest risk (59.9%).

Other risk factors for OA are genetic predisposition (for instance, due to chondrodysplasias caused by collagen mutations, hemochromatosis, and familial calcium pyrophosphate crystal deposition [CPPD]) as well as congenital or acquired malalignment of joints. In addition, any prior joint damage due to injury or another form of arthritis, may result ultimately in OA. Mineralization of articular cartilage is nearly universal in OA, but the primary mineral is basic calcium phosphates (BCPs) rather than CPPD. BCP deposition is an indissociable process of OA and does not characterize a specific subset of the disease. Calcium containing crystals may contribute to inflammation in OA tissues through their direct interactions with components of the innate immune system, as well as by inducing or amplifying other inflammatory signals.

**Moving Toward a Better Understanding of Osteoarthritis Pathogenesis**

Is OA primarily a disease of wear and tear that is caused by mechanical forces or one driven by inflammation causing an imbalance in cartilage degradation and synthesis, with degradation overwhelming the synthetic repair in the joint? Until recently, the causes of OA were thought to be primarily mechanical, and many still believe this to be true. It has become increasingly clear, however, that OA is not a single disease, but rather the clinical end point of numerous disorders leading to the eventual failure of one or more joints of the body as a manifestation of a common final pathway linking mechanical, biochemical, and inflammatory components.

Although OA is most often diagnosed at the radiographic stage, there is evidence from other imaging modalities, including ultrasonography and MRI, that indicates there are stages of joint damage that precede radiographic change. For example, while moderate to large synovial effusions may be identified by physical examination or, in some cases, routine plain radiography, more often detection of the limited synovitis characteristic of OA necessitates the advanced imaging techniques of MRI or ultrasonography.

These imaging techniques may also detect synovial thickening, which can be independent of effusion and which correlates well with histological changes, including
inflammatory cell infiltration and synovial lining hyperplasia. Using MRI, changes in matrix composition and alterations in subchondral bone marrow can be detected.

To improve understanding of disease pathogenesis and application to clinical practice, it is useful to consider OA in the context of other chronic disease paradigms. Consider the example of cardiovascular disease; it can be incited by hypercholesterolemia that initiates a silent disease process of atherosclerosis. This can evolve to a symptomatic stage manifested by angina and result in major end stage events such as stroke, heart attack, or heart failure. Applying such a paradigm to OA, these would be represented by the initiation of disease at a silent molecular and serologic level—at which time the opportunity for effective intervention would be greatest—followed by preradiographic and then radiographic stages, and culminating in “joint death” and replacement. Seeing OA as a continuum may help drive the search for effective interventions at earlier stages of the disease. (Figure 2)

**Figure 2.** Stages of Osteoarthritis Development

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A Joint Disorder with an Inflammatory Component

While often described as a disease of the cartilage, OA is best characterized as a “whole joint” disorder. This clinical syndrome affects not only the articular cartilage, but also other joint tissues such as the synovium, bone, ligaments, supporting musculature, and fibrocartilagenous structures, such as the meniscus. It is necessary to understand the function and interaction of these tissues holistically.

This particular joint disorder appears to develop in the context of an inflammatory response. Looking at the disequilibrium hypothesis of OA—whereby the disease results from imbalances between the forces of degradation and those of synthesis within the cartilage—it is clear that a number of factors are involved in maintaining homeostasis in this tissue. On the degradation side are the proinflammatory cytokines (interleukin [IL]-1β, tumor necrosis factor [TNF]-α, IL-6, IL-8, IL-11, IL-17, and IL-11); the matrix metalloproteinases (MMPs) such as the collagenases, stromelysin, and the gelatinases; the aggrecanases, prostaglandins, nitric oxide, and complement components. On the synthesis side are the anti-inflammatory cytokines (IL-4, IL-10, and IL-13); tissue inhibitors of metalloproteinases (TIMPs); growth factors (insulin like growth factor [IGF]-1, transforming growth factor [TGF], basic fibroblast growth factor [bFGF], and bone morphogenetic proteins [BMPs]), and collagen and proteoglycan synthesis.

While it is increasingly evident that there is an inflammatory component to OA, it is also believed that this component drives disease progression and plays a role in the pain associated with the disease.

The Chronic Wound Healing Response

The new hypothesis concerning the pathogenesis of OA builds on these prior observations to propose that OA is a chronic wound healing response involving the innate immune system. The innate immune system is one of three levels of host defense (ie, anatomic barriers, innate immunity, and adaptive immunity). Specifically, the innate immune response is the rapid initial host response to conserved patterns in nature such as invading pathogens. Innate immune responses include complement, neutrophils, host defense peptides, dendritic cells, nod like receptors (NLRs), and Toll like receptor (TLR) pathways.

Emerging data support the current hypothesis that OA is a disease of innate immune system activation. The inflammatory response observed in OA and in traumatic joint injury bears a striking resemblance to the response to infection, involving many of the same components. Following acute "macroinjury" or subacute "microinjury" due to daily joint use, activators of innate immunity known as danger associated molecular patterns (DAMPs) are released, leading to immune responses in the joint that promote further cartilage degradation through their induction of proteolytic enzymes, thereby amplifying a vicious cycle of innate immune activation in OA. Mediators in this process, DAMPs link injury to immune responses and include hyaluronan and
fibronectin fragments,\textsuperscript{24,31} which activate TLRs and alarmins, and uric acid, which plays a possible role in macrophage related inflammasome activation in OA.\textsuperscript{24,33} Moreover, activation of the complement cascade, another component of innate immunity, is triggered in OA by degradation products of extracellular matrices of cartilage and other joint tissues.\textsuperscript{25} A recent excellent review focuses on how the mechanical process of acute, subacute, and chronic joint injury triggers an immune response and the subsequent state of chronic inflammation that results in propagation and progression toward the phenotype recognized as clinical OA.\textsuperscript{24}

In addition, macrophages play a major role as mediators of a chronic innate immune system response in OA and are found infiltrating the OA synovium and joint capsule.\textsuperscript{25,30} In this regard, OA appears to conform to a newly emerging concept of chronic disease pathogenesis. In this paradigm, macrophages fail to transition from a proinflammatory to an antiinflammatory phenotype,\textsuperscript{35} thus perpetuating a maladaptive inflammatory, joint tissue degradative “clean up” response. This chronic wound healing response is potentiated by a number of other factors, including age and BMI, and genetic factors that likely modulate the robustness of an individual's innate immune and joint tissue repair responses. Figure 3 presents a unified vision of the OA disease process.

\textbf{Figure 3.} Unifying Model of Osteoarthritis Pathogenesis. The Interacting Cogwheels, Able to Turn Intermittently, Depict the Penchant for Osteoarthritis Disease Activity to Wax and Wane Image used with permission from Virginia Kraus, MD, PhD.
The Pathogenesis of Osteoarthritis Symptoms

Symptoms associated with OA, such as morning stiffness or pain, can find their origins in the overall pathogenesis of the disease as well. The stiffness that occurs in OA after a night’s sleep or a period of inactivity is believed to be caused, in large part, by edema fluid accumulation in the periarticular tissues. Periarticular fluid retention is likely enhanced by hyaluronan that more readily escapes from the intraarticular space of the inflamed joint, which in the absence of activity, accumulates in the deep layers of the arthritic synovium. In a classic study of individuals with rheumatoid arthritis, the amount of hyaluronan appearing in the circulation in the morning in response to activity correlated with the duration of morning stiffness. In OA, serum hyaluronan also rises in response to first morning activity. Thus, it would appear that with joint movement, hyaluronan and edema fluid are mobilized from the tissue to the lymphatic system and circulation, resulting in improved synovial tissue compliance and improvement in joint stiffness symptoms.

Joint pain has multiple etiologies. Articular cartilage is both aneural and avascular. Cartilage damage may occur without pain, but the subchondral bone, periosteum, periarticular ligaments, periarticular muscles, synovium, and joint capsule are all richly innervated and are the source of nociception in OA. Pain is a sign that collateral damage is occurring. It is believed that changes in the bone and synovium, and, in particular, synovial effusion, are the primary causes of pain.

A New Definition of Osteoarthritis

Osteoarthritis can no longer be considered simply a disease of “wear and tear” or a natural consequence of old age. Research has provided a greater understanding of this all too common disorder. As a result, a new definition of the disease is proposed herein: Osteoarthritis is a disorder involving movable joints, characterized by cell stress and extracellular matrix degradation. It is initiated by acute macroinjury and subacute and chronic microinjury that activates maladaptive repair responses, including proinflammatory pathways of innate immunity, bone remodeling, and osteophyte formation.
References


