Overview

This monograph features an outstanding faculty of OA experts to review and debate the impact of research innovations and treatment developments. These innovations have the potential to transition current practice strategies from a symptomatic tactic to a more comprehensive disease treatment approach.

Osteoarthritis (OA) management is transitioning from a focus on symptom control to disease modification. Early detection and intervention are essential to this process. These changes in the clinical landscape have the potential to improve outcomes in a growing patient population that has jumped by more than one-third in the last decade, with nearly 27 million Americans now diagnosed.

Target Audience

This monograph is intended for rheumatologists, rheumatology fellows and other interested health care professionals.

Objectives

After completing this activity, the learner will be able to do the following:

• Identify epidemiologic changes in OA and discuss their impact on clinical practice;
• Assess efficacy and safety data from clinical trials of disease-modifying OA drugs (DMOADs) and gauge their potential impact on clinical practice;
• Discuss new and emerging pain modulators as they apply to management of patients with OA;
• Discuss the updated pathophysiology of OA.

Disclaimer

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Acknowledgement

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1. Read the monograph,
2. Log on to www.ccfcme.org/OAToday,
3. Complete the multiple choice post-test, evaluation, and registration form,
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<th>Faculty</th>
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<td>Abbott Laboratories Consulting; Educational grant support</td>
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The following faculty have indicated they have no relationship which, in the context of their presentation, could be perceived as a potential conflict of interest:

- Steven Abramson, MD
- Elaine Husni, MD
- Roland Moskowitz, MD

All other planners, CME staff, and content reviewers have no relevant financial relationship to disclose.
**Introduction**

The lifetime risk of developing symptomatic knee osteoarthritis (OA) has been estimated at 46%, which is more than double the lifetime risk of cancer, according to the Centers for Disease Control and Prevention. Currently, OA, the most common form of arthritis, affects more than 27 million people in the United States, and this number will swell with the aging of the baby boomer population.

The financial and physical burdens of arthritis are substantial. Direct costs attributable to arthritis and other rheumatic conditions total more than $80 billion in the United States. More than half of the direct costs occur in the outpatient setting. Musculoskeletal disorders represent the most frequent cause of disability in the world, according to the World Health Organization. The demand for primary hip and knee arthroplasty in the United States is expected to increase by 174% and 673%, respectively, by 2030.

Current therapeutic approaches to OA do not prevent the disease or its progression. Because pain control is often inadequate when OA progresses to a severe stage, the identification of individuals at high risk of OA and improvements in early detection and intervention are essential to improved management of the disease. The heterogeneous etiology of OA contributes to the challenge of treating it and finding effective disease-modifying drugs; furthermore, gaps in knowledge of the processes that lead to pain generation have slowed the discovery of new agents to alleviate pain.

On November 11, 2010, a symposium sponsored by the Cleveland Clinic Center for Continuing Education, held in Atlanta, brought together a faculty of OA experts to review and debate the impact of research innovations and treatment developments in OA. This publication is developed from that symposium.

**References**


**Osteoarthritis Epidemiology and Risk Factors – Who Gets It and Why**

Roland W. Moskowitz, MD

Definitions of OA have emphasized joint damage, especially articular cartilage loss, while giving less emphasis to the repair processes taking place in the joint, processes that attempt to contain damage caused by local mechanical insults. One current concept is that OA can be viewed as a disease of failed cartilage repair in which increased mechanical stress plays an important etiopathologic role.

The process in early OA involves release and synthesis of proinflammatory mediators and enzymes that degrade articular cartilage. As a result, chondrocytes fail to maintain homeostasis between extracellular matrix synthesis and degradation.

Besides collagens, the extracellular matrix contains proteoglycans, among other molecules. Collagens form a fibrillar mesh that provides resistance to shear and tension. While proteoglycans can be turned over, collagen loss is rarely, if ever, reversed, and leads to irreversible destruction of the extracellular matrix and disease progression.

As cartilage is lost, the progressive release of chondrolytic and proteolytic enzymes results in loss of joint space. Chondrocytes proliferate in an attempt to repair the damaged articular cartilage. The synovial inflammatory reaction in the joints of patients with OA perpetuates joint breakdown. The pathology leads to a loss of cartilage and bone in the entire joint area.

**EPIDEMIOLOGY: MOST HAVE OA BY AGE 65**

Radiographic evidence of OA exists in most people by age 65; and in 80% of those older than 75 years. OA is second only to ischemic heart disease in causing disability in men older than 50 years, and it accounts for more hospitalizations than rheumatoid arthritis each year.

The Johnston County (North Carolina) Osteoarthritis Project, a population-based longitudinal study of more than 3,200 residents aged 45 and older, determined the lifetime risk of symptomatic knee OA to be 44.7%. It is anticipated that nearly half of the adults in Johnston County will develop symptomatic OA by age 85.
Classification criteria have been developed for OA of the hand, hip, knee, and are based on symptoms, clinical findings, and radiographic and laboratory features. The criteria are summarized in Table 1.\(^4\)\(^-\)\(^6\)

### Classification and Presentation

Classification criteria have been developed for OA of the hand, hip, knee, and are based on symptoms, clinical findings, and radiographic and laboratory features. The criteria are summarized in Table 1.\(^4\)\(^-\)\(^6\)

#### Table 1. Osteoarthritis classification criteria

**Hand**

<table>
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<tr>
<th>Pain, aching, or stiffness and at least 3 of the following 4 features:</th>
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<tr>
<td>• Hard tissue enlargement of 2 or more of 10 selected joints*</td>
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<tr>
<td>• Hard tissue enlargement of 2 or more distal interphalangeal (DIP) joints</td>
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<tr>
<td>• Fewer than 3 swollen metacarpophalangeal (MCP) joints</td>
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<tr>
<td>• Deformity of at least 1 of 10 selected joints*</td>
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*10 selected joints: second and third DIP, second and third proximal interphalangeal (PIP), and first carpometacarpal (CMC) joints of both hands.

**Hip**

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<th>Pain and at least 2 of the following 3 features:</th>
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<tr>
<td>• ESR &lt; 20 mm/hr</td>
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<tr>
<td>• Radiographic femoral or acetabular osteophytes</td>
</tr>
<tr>
<td>• Radiographic joint space narrowing (superior, axial, and/or medial)</td>
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**Knee**

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<th>Pain, tibiofemoral osteophytes, and at least 1 of the following 3 features:</th>
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<tr>
<td>• Age &gt; 50 years</td>
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<tr>
<td>• Stiffness &lt; 30 minutes</td>
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<td>• Crepitus on examination</td>
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Although some people have generalized OA involving multiple joints, localized OA is a more common presentation. When OA is localized to the knee, bilateral presentation is more common than unilateral, but the opposite is true when OA involves the hip. In the hand, OA usually affects rows and rays in a given pattern, and disease is usually more severe in the dominant hand.

#### Risk Factors

Major risk factors for the development of OA can be divided into general and local factors.

**General Factors**

As shown in the Johnston County Osteoarthritis Project,\(^3\) the likelihood of OA increases with age. The incidence and prevalence of OA is higher in women than in men, especially after age 50. In both men and women, the prevalence of severe OA increases logarithmically with aging (Figure 1).

**Aging**

Aging is accompanied by degenerative changes associated with the formation and accumulation of advanced glycation end-products (AGE) in cartilage; this changes the mechanical properties of the cartilage, causing it to stiffen.

**Genetic mutations**

Genetics plays a major role in OA development, age at which it presents, sites of involvement, disease severity, and rate of progression. Clinical manifestations of OA have been described in families with a single-base mutation, arginine519 to cysteine, in the type II procollagen gene.\(^7\) The cysteine substitution caused a generalized OA over several generations in these families; 11 known families have been described with this substitution.

A COL2A1 glycine substitution in the triple-helical domain of type II collagen has recently been described in two Australian families who presented with an isolated arthritis phenotype before age 30.\(^8\)

**Obesity**

Obesity is a risk factor for incident knee OA and is also associated with an increased risk of progression in knees with varus (bow-leg) but not with valgus alignment (knock knees).\(^9\) Thus, weight loss, although it is generally considered a strategy to prevent OA development and to ameliorate OA symptoms, may not prevent OA progression in varus knees.

Nevertheless, weight reduction is associated with small improvements in both pain and functional limitation in
obese patients with knee OA. Each pound of body weight translates to a three- to five-fold increase in stress across the knee, so weight loss remains an important strategy to relieve symptoms and limit disease progression.

Squatting and bicycling
Prolonged squatting and bicycling are physical activity risk factors for OA. Knee bending is associated with a border-line increase in the risk for OA. Climbing stairs and walking up/down hills has not been shown to increase OA risk. Recreational running has not been consistently associated with knee OA development; however, running in the presence of significant knee abnormalities such as varus or valgus deformities or morbid obesity may have a negative impact on symptoms and disease progression.

Leg length inequality
Leg length inequality has a major effect on the risk of OA: a leg length inequality of 1 cm or more increases the risk of OA symptoms and OA progression in the shorter leg. Appropriate lifts to equalize leg length may modify OA.

Local Factors
Major local factors for OA include joint injury, deformity, inflammation, and overuse.

Meniscus tear
Joint injury, such as torn meniscus, is associated with a greater likelihood of developing OA. In experimental studies, rabbits undergoing partial meniscectomy developed pitting and ulceration of the joint 6 to 12 weeks following the resection, with formation of osteophytes. Continued use of the joint (treadmill running for 15 minutes twice daily) resulted in further secondary osteoarthritic changes and synovial inflammation.

Anterior cruciate injury
The prevalence of knee OA is 13% among individuals with injuries to the anterior cruciate ligament. The prevalence rises further when medial meniscus injury is present.

Joint morphology
The morphology of the joint contributes to OA risk. A varus thrust is associated with a four-fold increase in the risk of medial knee OA progression. A valgus thrust, which is less common than a varus thrust, also affects the pattern of knee involvement.

The infrapatellar fat pad can contribute to knee OA. In OA, levels of interleukin-6 and the expression of its receptors are increased compared with normal subcutaneous adipose tissue, which may contribute to cartilage damage.

RISK FACTORS FOR PROGRESSION
The risk factors for progression of OA are similar to those for the development of the disease. They include female gender, overweight, abnormal femoral head geometry, malalignment, quadriceps weakness, ligamentous laxity, and meniscal tears.

CONCLUSION
Osteoarthritis is common and becomes more so with aging. Its risk factors and epidemiology are well defined. Addressing modifiable risk factors, such as obesity and certain physical activities, can potentially prevent and slow progression of the disease.

REFERENCES
Judicious end point selection in clinical trials of OA treatments is critical to assess the true impact of interventions in this disease. This article reviews the current symptomatic and radiographic endpoints being used in OA clinical trials, emerging imaging modalities and end points that enable the measurement of changes in cartilage morphology in an attempt to establish more meaningful endpoints, and biomarkers that may one day be used to identify the effects of treatment on the pathogenic process of OA.

**OA IS A HETEROGENEOUS DISEASE**

The timeline for the pathogenesis of OA influences the timing of intervention to control symptoms, prevent disease, or slow its progression. Before a patient begins to exhibit symptoms or radiographic evidence of OA, he or she may have genetic susceptibilities, various forms of mechanical stressors, or triggers that turn on the disease process. The clinical (radiographic) phase begins when a mediator or genetic or structural accelerator/propagator causes disease progression. The onset of the radiographic changes may or may not coincide with the onset of clinical signs and symptoms.

Osteoarthritis is not solely a disease of cartilage. The joint can be considered as an organ that has multiple components consisting of cartilage, bone (osteophytes and subchondral bone), synovium, joint capsule, muscle, tendons and ligaments, the bursae around the joints, and peripheral and central nerves. Abnormalities in any of these components can cause symptoms, but which are responsible for symptoms may vary.

Because OA affects a number of different joints, each with potentially different biomechanical drivers and or biochemical and pathophysiologic processes, a drug that is effective in one location (eg, hand OA) may not be effective in another (eg, spine OA). Therefore, drugs may need to be studied in different disease processes, each of which may require its own outcome measurements and study design.

**OUTCOMES MEASURES USED TO DEFINE A RESPONSE TO TREATMENT**

Outcomes selected as end points in OA clinical trials reflect aspects of the disease that can be measured to distinguish differences between a treatment and an active comparator or a placebo. For example, instruments that measure levels of or changes in pain, function, and stiffness serve as the basis for criteria to evaluate how a treatment affects OA symptoms. Other criteria to determine response to treatment incorporate outcomes such as disability, quality of life, the rate of structural progression of the disease, joint failure, and disease development.

Pain relief is an important outcome measure that is used to evaluate a drug’s effect on OA signs and symptoms. The designs of studies to assess pain relief often do not reflect clinical practice; in most studies, patients must discontinue analgesic medications and only those who demonstrate a worsening of their symptoms (eg “flare”) following treatment withdrawal are enrolled into the clinical trial. With this study design, endpoint measures are compared with baseline measures taken after washout of prior medications and subsequent flare of symptoms. The standard measure of pain for OA of the knee and hip is the 5 pain questions of the WOMAC index.

The Osteoarthritis Research Society International (OARSI) and the Outcome Measures in Rheumatology (OMERACT) group have developed responder criteria designed to better detect differences between treatments studied in clinical trials. By the OMERACT-OARSI criteria, a response is defined as a composite outcome of an improvement in pain or function combined with an absolute change in these measures of at least 20 mm (on a 0- to 100-mm interval scale) or improvements of at least 20% and absolute changes of at least 10 mm on at least two of the following: pain, function, and patient global assessment.

**Challenges in Selecting Outcomes Measures**

The commonly used study design, in which the main outcome measure is change in OA symptoms, presents several challenges:

- Patients with OA have intermittent exacerbations of pain and day-to-day (and within-a-day) variability.
- Placebo benefits, which can be substantial and sustained in OA, must be considered.
- For entrance into a study, patients must have moderate to severe levels of baseline pain for treatment effects to be demonstrated.
- Failure to relieve pain can lead to a substantial number of study dropouts.
- The use of rescue medications in the event of a flare can blunt the ability to observe a response.

As an example of the degree of placebo response possible in a clinical trial of treatments for OA, 60% of patients randomized to oral placebo in the Glucosamine Arthritis Intervention Trial (GAIT) achieved the primary outcome measure of a 20% decrease in knee pain from baseline to 24 weeks. The placebo response is also large in clinical trials of intra-articular therapies; in a placebo-controlled
randomized trial of intra-articular injection of hyaluronic acid, patients randomized to receive placebo had a 0.69 decrease from baseline in the pain component of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index over 26 weeks, compared with a decrease of 0.84 in the group assigned to active treatment, for an effect size of 0.15. A clinically relevant placebo benefit can appear soon after initiation and may be maintained for as long as 2 years as seen in both the GAIT study as well as Knee OA Structural Arthritis (KOSTAR) study. In monitoring pain over the course of a day, tremendous variability in pain from hour to hour has been reported (Figure 1). The level of pain also may vary on the day of the week, with more variability generally reported on weekdays compared with weekends.

A different set of difficulties arises when attempting to study the effect of a therapy on structural progression of disease. Current guidance from the US Food and Drug Administration (FDA) dates to 1999 when the FDA proposed a change in joint space narrowing using knee or hip radiographs to demonstrate slowing of cartilage loss in clinical studies of at least 1 year. Recommendations for revisions of these guidelines have been submitted and include information on the consideration of other imaging endpoints such as magnetic resonance imaging (MRI).

When radiographic change is considered an outcome measure, a trial duration of 1 to 3 years is required to detect differences between treatments, whereas symptom studies can be as short as 12 weeks. Therefore, patients participating in trials that measure radiographic change will need to be maintained on their assigned therapies over the long term to demonstrate changes in structural progression. In order to enable participant retention, they must also be permitted to use therapies that treat their symptoms, because therapies that modify structure may not have an impact on symptoms. The optimal study population to test a drug’s effect is also controversial, as the effect may be different at different stages of disease (early, established, end stage).

The optimal joint to study is also under question. Some data suggest that the hip is superior to the knee because disease progresses more rapidly at the hip and any differences between treatments may be more apparent at the hip sooner than at the knee.

The ideal imaging method to assess structural change has also not been agreed upon. Measuring OA progression with plain radiographs in clinical trials involves meeting several requirements. One such requirement is standardized joint positioning, as differences in joint position affect joint space measurement. In some studies, the measurement error of the technique has exceeded the observed mean changes in joint space. Factoring in the measurement error has gained favor by OARSI when evaluating disease progression. When using plain radiographs to measure progression, one must also consider that the cause of joint space narrowing may be multifactorial, and may not reflect rapid loss of cartilage but rather meniscal extrusion or degeneration.

In the KOSTAR study, using three times the standard deviation in change from baseline in joint space width to define definite disease progression yielded a small number of patients (10% to 13%) with disease progression at 2 years.
NEWER IMAGING MODALITIES TO ASSESS STRUCTURAL CHANGE

Newer technologies may help to identify disease progression earlier, when intervention may be more effective. Identifying patients with fast progressing disease through more sophisticated imaging may permit including them in pharmacologic intervention trials that would allow for studies of shorter duration to determine an intervention’s effect on structural changes.

Magnetic resonance imaging using high precision scanners is being used to measure bone marrow lesions, cartilage volume, and cartilage thickness. Bone marrow edema lesions on MRI have been found in patients with knee OA who are experiencing pain. Bone marrow lesions are also associated with an increased risk of cartilage loss in the associated compartment and predict subregional cartilage loss even when adjusting for the presence of other types of bone lesions in the same subregion. Because bone marrow lesions in the knee are reversible, they may represent a target for interventions in an effort to slow knee osteoarthritis progression.

Quantitative measurement of cartilage morphology using MRI provides information beyond joint space narrowing based on x-rays that may or may not reflect actual cartilage loss (eg, meniscal extrusion may also be seen as “joint space loss”). An aggregation of measures of cartilage thickness, cartilage volume, and cartilage metabolism obtained through various imaging techniques may better elucidate the complex disease process of osteoarthritis compared to measuring changes in osteophyte size and joint space width.

CONSIDERATIONS IN THE SELECTION OF BIOMARKERS

Osteoarthritis biomarkers are objective indicators of biologic and pathogenic processes. Biomarkers can be classified as diagnostic, burden of disease, prognostic, efficacy of intervention, and investigative. Worth considering is whether a biomarker reflects a single joint or total body burden of OA, if therapy directed at one part of the joint organ leads to changes in biomarker levels of another compartment, and which biomarkers are most relevant to structural changes. Also, serum and urine levels of biomarkers vary throughout the day and may be affected by physical activity, so standardized collection of samples may be necessary if using biomarkers to evaluate interventions in OA.

One biomarker shown to be independently associated with radiologic progression of OA is urinary C-terminal cross-linking telopeptide of type II collagen (CTX-II), which is a marker of cartilage degradation. Subjects with low baseline levels of this biomarker, or a reduction in levels after 6 months of treatment with risedronate, were associated with decreased radiographic progression of knee OA compared with subjects with persistently high levels.

PITFALLS TO TOTAL JOINT REPLACEMENT AS A “HARD” OUTCOME

Total joint replacement has been proposed as an outcomes measure, but this outcome is fraught with problems, including the large number of patients it would require to be enrolled in clinical trials of long duration and factors other than pain, function, and radiographic changes that can enter into the decision to do joint replacement (ie, access to care, patient tolerance to pain, surgeon bias, insurance/health care system). Instead, OMERACT and OARSI are advocating the development of criteria using a combination of symptoms and radiography that would serve as a surrogate end point to qualify a patient for a “virtual” total joint replacement.

CONCLUSION

Although current measures used to assess symptomatic outcomes in OA clinical trials can demonstrate differences between treatments, these may lack ideal discriminatory features with high baseline placebo responses and may not be reflective of responses in clinical practice. Similarly, the currently available outcomes to measure radiographic progression using plain radiography are limited by the small number of patients overall who demonstrate detectable and relevant changes over time. Ongoing research into newer outcome measurements for clinical study designs may allow for superior assessment of the impact of an intervention in OA. Such measures are needed to allow the evaluation of novel therapies that address the biology of the disease.

REFERENCES


A significant unmet need in the treatment of OA is pharmacotherapy that has strong evidence of disease-modifying activity. Currently available analgesics used chronically for the symptomatic treatment of OA have limited effectiveness and side effects are prevalent.

The goals of therapy in OA are to provide effective pain relief, improve function, and ideally, slow, halt, or reverse disease progression. To achieve disease modification, a better understanding of clinical and molecular phenotypes of OA is needed; OA is not a single disease but one of heterogeneous etiologies (ie, aging, trauma, Kashin-Beck disease, Paget’s disease, obesity) that takes decades to develop.

**MOLECULAR MECHANISMS CONTRIBUTE TO OA PHENOTYPE**

**Clinical Phenotypes**

Currently, phenotyping of OA is based on clinical characteristics and is defined by primary vs secondary OA, a history or absence of trauma, the presence or absence of metabolic diseases that predispose to OA or deposition of crystalline calcium pyrophosphate dihydrate, the number of joints affected (single vs generalized OA), and the specific joints affected.

**Molecular Phenotypes**

Several early molecular mechanisms contribute to OA phenotypes. A genetic predisposition to OA is evident. Genetics influence susceptibility to OA through diverse pathways and at different stages of disease (Figure 1).

**PROTEOGLYCAN LOSS OCCURS EARLY IN OA**

OA is a disease of all compartments of the joint — cartilage, bone, and synovium. Multiple enzymes have been implicated in the pathogenesis of this complex process. In many patients, the earliest change appears to be proteoglycan loss within the articular cartilage, followed by degradation of type II collagen and abnormalities of bone, synovium, and the entire joint.

Strategies to block degradation of cartilage focus on interruption of proteoglycan loss, acting at the enzymes ADAMTS5 or ADAMTS12, or inhibition of degradation of...
collagen, particularly at the target of matrix metalloproteinase 13 (MMP-13). These strategies are all under investigation as targets for early pharmacologic intervention in OA.

**COLLAGEN FRAGMENTATION: TYPE II COLLAGEN RECEPTOR IS ACTIVATED IN EARLY OA**

Discoidin domain receptor 2 (DDR2) is another potential early therapeutic target under investigation. DDR2 is a cell surface type II collagen receptor whose expression is increased when MMP-13 expression is upregulated. Evidence suggests that at an early stage of OA, DDR2 stimulates chondrocytes to synthesize and release MMP-13 prior to the occurrence of significant cartilage degradation. In models of OA and human OA hip joints, expression of DDR2 and MMP-13 are both increased in articular cartilage.

**BONE AS A TARGET FOR DISEASE-MODIFYING THERAPY**

Preventing remodeling of bone may also be a disease-modifying pharmacologic target. Bone remodeling and bone turnover refer to the ongoing process by which new bone is created. Osteoclasts resorb old bone tissue and osteoblasts form new bone tissue. Genetic variations among molecules involved in bone remodeling also determine susceptibility to OA. Bone resorption and bone formation are normally in balance, but in OA, imbalances in subchondral bone turnover can lead to thickened, low-quality bone, contributing to cartilage loss and joint space narrowing. In addition, trabecular bone becomes thinner, and cytokines, growth factors, and other mediators derived from subchondral bone may promote cartilage catabolic processes.

Regulation of osteoblast and osteoclast activation may represent a novel approach to treating OA. Bisphosphonates, calcitonin, strontium, and cathepsin K may have the potential to act as disease-modifying agents in OA.

**BONE-SYNOVIAL INTERPLAY IN OA**

Bone and synovium interact in OA. Synovial inflammation may arise initially from fragments of cartilage that activate the synovium to release inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF). Macrophages that are present in large quantities within the chronically inflamed synovium secrete angiogenic factors, such as vascular endothelial growth factor, that lead to neovascularization.

An early microscopic feature of OA is the formation of new blood vessels, and these new blood vessels are innervated. One of the unknowns in OA is the source of pain, since cartilage lacks nerve endings. The speculation is that neovascularization may contribute to nociception. With neovascularization, molecules from bone may penetrate into the cartilage and aggravate the disordered catabolic state of chondrocytes within cartilage.

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**Figure 1. Pathways for development of osteoarthritis**

Figure shows how genetics can influence the development of osteoarthritis through diverse pathways and at different stages of the disease.
Sources of Inflammatory Mediators: Synovium, Cartilage, Bone

The inflammation in OA is local as opposed to systemic, as the sources of inflammatory mediators in OA are the bone, synovium, and the cartilage. Cytokines, inflammatory cells, and complement are produced within the synovium, bone, and the cartilage. For many years, IL-1 and TNF were thought to drive the catabolic changes within cartilage.

ARE BONE MARROW LESIONS AN IMPORTANT THERAPEUTIC TARGET?

Improvement in bone marrow lesions following one rheumatologist’s self-treatment of OA with a fully human TNF antibody prompted the initiation of clinical trials of TNF inhibitors in patients with hand OA. Caution is warranted in using bone marrow lesion improvement as an indicator of efficacy in OA, however. Spontaneous waxing and waning of bone marrow lesions occurs in about 20% of cases, although typically these lesions will progress. In addition, bone marrow lesion progression may be a reliable surrogate of disease progression in the joint cartilage and other joint tissues. Therefore, an agent’s ability to reverse bone marrow lesions may be insufficient to prevent disease progression.

ARDUOUS PROCESS TO DISEASE-MODIFYING DRUG DEVELOPMENT

The pathway to market for a disease-modifying OA drug is prolonged and expensive, and it rarely succeeds. The process first requires validation of a target through in vitro, ex vivo, and animal models, followed by a difficult clinical development program. Potential problems in targeting disease structure modification as an outcome measure are the large number of subjects needed and the long duration of clinical trials required to demonstrate superiority on this end point, the cost of imaging studies to measure this outcome, and the possibility that the drug will not affect symptoms, which may limit its uptake in the market.

Tens of millions of dollars were invested in the risedronate clinical trial program; the result—failure of risedronate to demonstrate superiority over placebo on the primary outcome measure—may have occurred because the number of disease progressors enrolled was insufficient to show a significant effect. Consequently, several pharmaceutical manufacturers have abandoned their OA disease-modifying development programs in order to direct their resources to agents that offer superior pain relief, which can be accomplished in as little as 3 months in a clinical trial.

As a consequence of the daunting pathway to approval of a disease-modifying OA drug, interest has emerged in biomarker end points that can detect preradiographic abnormalities, with the potential for intervention to prevent the earliest abnormalities in OA and prediction of structural outcomes. The desired strategy is to identify and validate imaging, biochemical, or genetic biomarkers, and assess an agent’s impact on these biomarkers in studies of a few months’ duration before embarking on a robust clinical development program. The problem is difficult to solve, however, given the heterogeneity of OA etiology and the specific molecular targets within each phenotype of OA.

By the time OA reaches the clinical stage, multiple molecular and histologic pathways have likely been activated, rendering intervention unlikely to modify the disease. The challenge lies in intervening upon an appropriate molecular pathway early enough to affect the disease process.

SUMMARY

Osteoarthritis is potentially modifiable. To move the field of disease-modifying OA agents forward, better characterization is needed of clinical phenotypes and the natural history of the disease, as well as a better understanding of the early molecular mechanisms that differentiate clinical phenotypes. Imaging, biochemical, and genetic markers that differentiate clinical phenotypes, especially slow progressors vs. fast progressors, and surrogate end points for clinically significant disease progression must also be validated.

REFERENCES

Pain is an important contributor to the functional limitations, impaired quality of life, and psychological distress that osteoarthritis patients experience. Over and above the difficulty in developing disease-modifying OA drugs is the attempt to alleviate pain in patients with OA. This article will describe the basis of pain in OA, the pathways by which pain signals are transmitted, and new approaches to modulate pain beyond traditional analgesic and anti-inflammatory medications.

**PAIN GENERATION AND THE NEUROBIOLOGY OF THE JOINT**

An understanding of how pain is generated in OA is essential in attempts to enhance pain relief. The joint contains a variety of sensory nerves. Large-diameter myelinated fibers are responsible for transmission of proprioception, which can be interpreted as either motion or position, whereas small-diameter unmyelinated fibers (C fibers) mediate the pain sensation. Slightly larger myelinated fibers have an unmyelinated “free” nerve ending (A delta fibers), and these fibers transmit painful stimuli. C fibers and A delta fibers constitute most of the sensory neurons in the peripheral nervous system.

**Mechanical and inflammatory factors in pain**

Joint nerve fibers are activated by mechanical factors. Intra-articular fluid injection increases intra-articular pressure and the discharge rate of articular afferents. In situations of acute trauma, such as with injury to the anterior cruciate ligament, mechanosensitized gated channels are activated and neuropeptides (ie, substance P, calcitonin gene-related peptide, vasoactive intestinal peptide, nerve growth factor) are released, stimulating the activation of peripheral nociceptors.

Other inflammatory mediators, such as eicosanoids, are involved in the generation of pain in OA. The prostaglandins are the most comprehensively studied of the eicosanoids. Injection of prostaglandin (PG)I2, PGE1, and PGE2 has been found to sensitize joint afferents and propagate afferent firing rate in response to noxious mechanical and chemical stimuli.

Activation of ion channels located on the terminals of nociceptors is one means for initiating nociceptive processing. Sodium channel expression and sodium channel currents are upregulated with chronic inflammation, and activation of voltage-gated calcium channels enhances neuronal firing rate; therefore, sodium channels and calcium channels are targets for the development of drugs to inhibit pain.

Transient receptor potential (TRP) channels are another family of ion channels. The TRP vanilloid channel 1 receptor, which is activated by heat, is another ion channel pathway of interest in drug development for inhibiting pain in OA. Its blockade has been successful at relieving nociceptive pain, but it has resulted in central hyperthermia.

Activation of cannabinoid receptors is a potential avenue to affect pain generation and perception, as these receptors, found peripherally (CB1) and centrally (CB2), modulate transmission of nociceptive signals.

**THE PAIN PATHWAY**

The nociceptive pain pathway is depicted in Figure 1. The initiating factors in OA occur peripherally in tissues in and around the joint. Signals generated by noxious stimuli — mechanical or inflammatory — are transmitted to the dorsal horn via cell nuclei in the dorsal root ganglion. From the dorsal horn,
these signals traverse the ascending pain pathway (principally, though not exclusively, the spinothalamic tract) to the brain. A descending pathway that is inhibitory in nature has recently been identified; descending signals can modulate activity in the dorsal horn by controlling spinal pain transmission.

**Peripheral Sensitization**

Sensitizing peripheral afferents lowers the activation threshold of joint nociceptors so that innocuous stimuli can elicit pain (allodynia) and noxious stimuli produce hyperalgesia. Because prostaglandins are known to sensitize peripheral neurons, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase inhibitors, which inhibit prostaglandin production, reduce sensitization to stimuli and, therefore, are effective at reducing pain in OA.

**Pharmacologic therapy directed at peripheral pathway**

Preliminary data suggest that therapies directed against nerve growth factor and its neuronal receptors could have analgesic potential because nerve growth factor modulates pain signaling pathways through nociceptor sensitization. Nerve growth factor is released upon injury and interacts with the high-affinity receptor TrkA, which is present on peripheral neurons, C fibers, and A delta fibers. Nerve growth factor also interacts with mast cells upon the release of bradykinin and histamine. Nerve growth factor interaction at the TrkA receptor and the release of bradykinin and histamine sensitize peripheral neurons; this sensitization is believed to be the mechanism by which nerve growth factor plays a role in mediating pain, and by which its antagonism may reduce pain.

A humanized monoclonal antibody to nerve growth factor — tanezumab — is under development for the treatment of osteoarthritic pain. Studies in animal models of OA and phase I trials in humans demonstrated efficacy of tanezumab in preventing or reducing pain in OA. This early success led to a phase II proof-of-concept trial; subjects were individuals in whom NSAIDs failed to control pain and candidates for joint replacement surgery, the goal being to study a population with severe OA. Patients were randomized to receive placebo or one of five dosages of tanezumab (10, 25, 50, 100, or 200 µg/kg body weight). Tanezumab or placebo was administered intravenously on day 1 and again on day 56. Patients enrolled had a mean age of 60 years, 60% were women, and the mean Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score at baseline ranged from 62.1 to 69.2 in each of the randomized groups.

The mean change in walking knee pain on a visual analog scale (VAS) from baseline to week 16 declined significantly more in all tanezumab groups when compared with placebo (P < 0.001 for all tanezumab groups vs placebo), with higher tanezumab doses being more effective than the lower doses. The Osteoarthritis Research Society International (OARSI) and the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) criteria were also used to assess response. The percentage of patients who achieved a response using the OMERACT-OARSI criteria was also significantly greater in patients randomized to tanezumab compared with placebo (P < 0.001 for all tanezumab groups vs. placebo). More than 93% of patients randomized to either 100 or 200 µg/kg met the OARSI-OMERACT criteria for response. No organ-specific safety signals were detected with tanezumab, with the exception of abnormalities of peripheral sensation (an increased incidence of paresthesias), which were particularly apparent with the two highest tanezumab doses. These events were self-limited and of relatively short duration; no permanent neurologic damage occurred in any subject.

A phase III program in OA was initiated and later put on clinical hold when radiographic evidence of bone necrosis was reported in 16 patients who had worsening OA and increased pain, all of whom had been randomized to tanezumab and who later required total joint replacement. A separate ongoing phase III study of tanezumab in patients with OA of the hip found no difference in the rate of total joint replacement across all treatment groups including placebo.

**Central Sensitization**

Activation of the peripheral nervous system promotes changes in neuronal structure and cellular metabolism at the level of the dorsal root ganglion and also the dorsal horn. These changes result in what has been termed central sensitization that occurs at the spinal cord and the cerebral cortex. Additionally, there are descending neuronal pathways from regions in the brain and brainstem that can also modulate activation of spinal cord neurons and have an effect on pain perception. Drugs such as serotonin/norepinephrine reuptake inhibitors are believed to relieve pain by affecting these pathways.

**Pharmacologic therapy directed at central pathway**

Duloxetine is a centrally acting drug in the serotonin norepinephrine reuptake class. It has been shown to be effective in a number of painful conditions and is approved by the US Food and Drug Administration (FDA) for the treatment of diabetic neuropathy, fibromyalgia, and, most recently, chronic musculoskeletal pain based on clinical trials conducted in patients with chronic low back pain and OA.

In two 13-week randomized, double-blind, placebo-controlled studies, Chappell et al studied duloxetine as an adjunctive treatment with NSAIDs or acetaminophen in patients with chronic OA knee pain despite their current treatment. In both studies, patients were started on either placebo or duloxetine, 30 mg/day, which was titrated to 60 mg/day after 1 week. In one study, patients were re-randomized to receive 60 mg or 120 mg of duloxetine; in the second study, the dosage could be increased to 120 mg/day only in the case of an inadequate pain response to 60 mg/day.

In both studies, statistically significant differences were observed between duloxetine and placebo in the prespecified primary outcome measures (Figures 2 and 3) as well as in most, though not all, of the commonly used endpoints for OA trials. Increasing the dosage of duloxetine beyond 60 mg/day did not appear to provide meaningful additional pain relief.
Because duloxetine is already approved for the treatment of several disorders, its side effect profile is known. In studies of patients with OA, adverse events that occurred more frequently compared with placebo were nausea, fatigue, somnolence, dizziness, hypertension, decreased libido, and constipation. Duloxetine can cause hepatotoxicity in the form of transaminase elevations, and, as with other antidepressants, the FDA warns of an increased risk of suicidal ideation in patients treated with duloxetine.

Chronic pain involves not only the periphery and spinal cord, but also the brain. In studies of chronic pain, characteristic regions of the brain are specifically activated. Some of these regions are the same as those activated in emotion-related tasks, such as fear and painful conditioning. Interestingly, the brains of chronic pain patients show atrophy (decrease in grey matter volume) in distinct locations, ones that are known to be involved in emotion-related tasks. Brain atrophy in patients with OA has been shown to be at least partially reversible by total joint replacement, which suggests that the nervous system also responds to the removal of a painful stimulus.

CONCLUSION

Pain in OA is initiated through activation of peripheral nociceptors and pain perception requires involvement of the brain. Repeated peripheral activation can lead to changes in neurons in the spinal cord and higher centers (central sensitization) which can modulate and perpetuate the pain response. Inhibition of peripheral input can effectively reduce pain in OA; interference with central pathways may also provide an effective means of reducing pain perception.

REFERENCES

Dr. Abramson: In 2008, OARSI published a literature review on pharmacologic treatments, and at that time, the effect size of acetaminophen was 0.21, whereas the effect size of NSAIDs was 0.32.1 Subsequently, additional randomized studies were conducted and OARSI issued an updated review in which the effect size of acetaminophen had narrowed.2 This update did not affect guidelines because some patients do respond to acetaminophen, but the effect size did shrink.

When opioids are used at high enough doses, their effect size is greater than 0.5, but it is clearly dose-dependent. Tramadol has an effect size similar to that of NSAIDs.

Dr. Moskowitz: We have to be careful about looking at effect size because it represents the difference in means between an experimental group and a control group. This may lead one to conclude that an agent is not effective, but the response can be significant for individual responders for whom a drug may be worthwhile as long as it is safe.

Dr. Bingham: Remember that effect size measurements are dependent upon the placebo response. The effect size is necessarily going to be smaller with a higher placebo response. A significant amount of research needs to be done on the placebo benefit and on which patients experience this benefit. One goal of future clinical trials should be to minimize the placebo effect so that we can see a true drug effect.

Dr. Husni: We are all very comfortable with oral NSAIDs, but we also have topical NSAIDs as well as opioids and tramadol. Can the panel weigh in on the practicality of combination therapy versus a more stepwise approach to inhibiting pain?

Dr. Bingham: From a study design perspective, what I like about the tanezumab study,3 as well as an older study with tramadol,4 was that it looked at a real-life situation in which patients were taking NSAIDs and still had pain, and then were randomized to add-on therapy, essentially a combination approach in an effort to gain additional benefit. The studies of duloxetine were conducted the same way.5,6 An unknown is whether topical application of an NSAID is an effective adjunct to systemic NSAID therapy. Only one topical NSAID (diclofenac) is FDA-approved for knee OA, and it has shown similar efficacy as oral therapies with fewer serious systemic effects.7,8 Two formulations are available: a gel and a solution containing dimethyl sulf oxide (DMSO). The DMSO solution is indicated for the treatment of signs and symptoms of osteoarthritis of the knee. The gel has approval for relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Recommendations from Osteoarthritis Research Society International1 list topical diclofenac as an effective adjunctive therapy; however, its long-term use is not well defined.9

Dr. Schnitzer: The concept of using multimodal analgesia is central to control of pain. The key here is not to add toxicity. To the extent that it’s feasible, multimodal analgesia makes a lot of sense, certainly from a basic science perspective and our understanding of the nervous system. Each of the agents you mentioned has a place depending on the patient’s presentation; generalizing the treatment approach is suboptimal because we treat individual patients who have individual needs.

Dr. Husni: The orthopedic side is doing a lot of this work. I find, at least at my institution, that they’re looking at individuals with focal OA injuries. These are not our population, so rheumatologists often do not see the patients who qualify for these studies.

Dr. Abramson: This is an exciting area of investigation that is moving forward with the utilization of mesenchymal stem cells, growth factors, and other types of technology. I’ve been doing work with biomedical engineers at our institution, and preclinical models have demonstrated exciting regenerative potential. This is far from ready for prime time but I think the future really is quite bright.

Dr. Moskowitz: The problem with stem cell technology is, if you are going to change the cellular component of a joint or cartilage, how do you sustain it, given mechanical and inflammatory alterations? It’s not just a matter of showing that you can make fetal cells or embryonic cells into adult stem cells. Wherever you put them, cartilage or bone, they need to be in an environment that allows unimpeded cellular response. We have made significant progress in this technology, but we still have a way to go.
**Question from audience:** I've given a lot of thought to patient acceptable symptom state (PASS). I take some exception to what you said about going from an 8 to a 6 on a 10-point pain scale being satisfactory pain improvement. If I don't get the patient below a 3, I don't feel that I've gotten the patient where I want to. Is there a way to structure clinical trials to emphasize patient-reported end points as the primary goals?

**Dr. Bingham:** We're beginning to incorporate more patient-reported outcomes within the Outcome Measures in Rheumatology (OMERACT) framework. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is an assessment of pain, function, and stiffness, but it is not a great assessment of one's ability to participate in valued life activities. A significant amount of work is needed in the area of patient-reported states. In OA, it's not just the pain quality, but also the impact of the pain that needs to be assessed.

**Dr. Husni:** The lag time for structural changes to occur in response to DMOADs is long. Are there any alternatives to total joint replacement that we can consider in the meantime? By 2030, the number of total joint replacements will be tremendous, and the morbidity with revision surgeries is real. Can retrospective epidemiologic studies assess the effects of DMOADs, or is total joint replacement an inevitable outcome?

**Dr. Moskowitz:** The Holy Grail is to find a DMOAD that will prevent the disease, reverse the disease, or at minimum, slow its progression. But until we find one, we have to treat the patient's symptoms. There are suggestions that agents such as glucosamine or avocado soybean inhibitors are disease-modifying, but the evidence is soft. The efficacy of total knee replacement is so dramatic that nobody argues whether it works or not. We have no agent that provides similar efficacy; that doesn't mean that we have to be pessimistic, but we may have to find a cocktail of agents that perhaps inhibits proteoglycanases as well as collagenases and stimulates repair. Disease modification studies are difficult due to limited methodologic approaches to demonstrate responses in a controlled fashion.

**Dr. Abramson:** Until now, the record keeping has not been robust enough in epidemiologic studies to get outcomes that can be trusted. As the use of electronic medical records becomes more widespread, virtual criteria that lead to total joint replacement can be developed. We must have more reliable databases in order to use population studies to obtain this kind of outcome. Databases will have to be programmed to pick up the virtual arthroscopy endpoint.

**Dr. Bingham:** The Osteoarthritis Research Society International (OARSI)-OMERACT initiative, included a study that tried to correlate patient characteristics with the surgeon’s decision to perform joint replacement; the results were a little disappointing in that there seemed to be no real-world predictor or relationship between the two factors.

**Question from audience:** Given the outcomes of the rabbit study that Dr. Moskowitz mentioned, what can we recommend to patients who appear to be at risk of overdoing exercise, such as patients with OA of the knee who want to run marathons?

**Dr. Moskowitz:** There’s no question that overuse of an osteoarthritic joint will promote inflammation and speed the disease along. But you can’t tell patients to sit in a chair and don’t do anything. You want to recommend exercises that strengthen muscles, such as quadriceps strengthening, straight leg raising, and isometric exercises that promote knee stability but don’t stress the knee.

There are ways to minimize deleterious effects of exercises and to protect the joint while still giving the patient exercises that will be beneficial and well-tolerated. Many mild exercises such as walking have been shown to be helpful for OA patients. If a patient has a severe valgus or varus, you may want to consider bracing or if their way of life is impaired, referral for orthopedic surgery.

**REFERENCES**


