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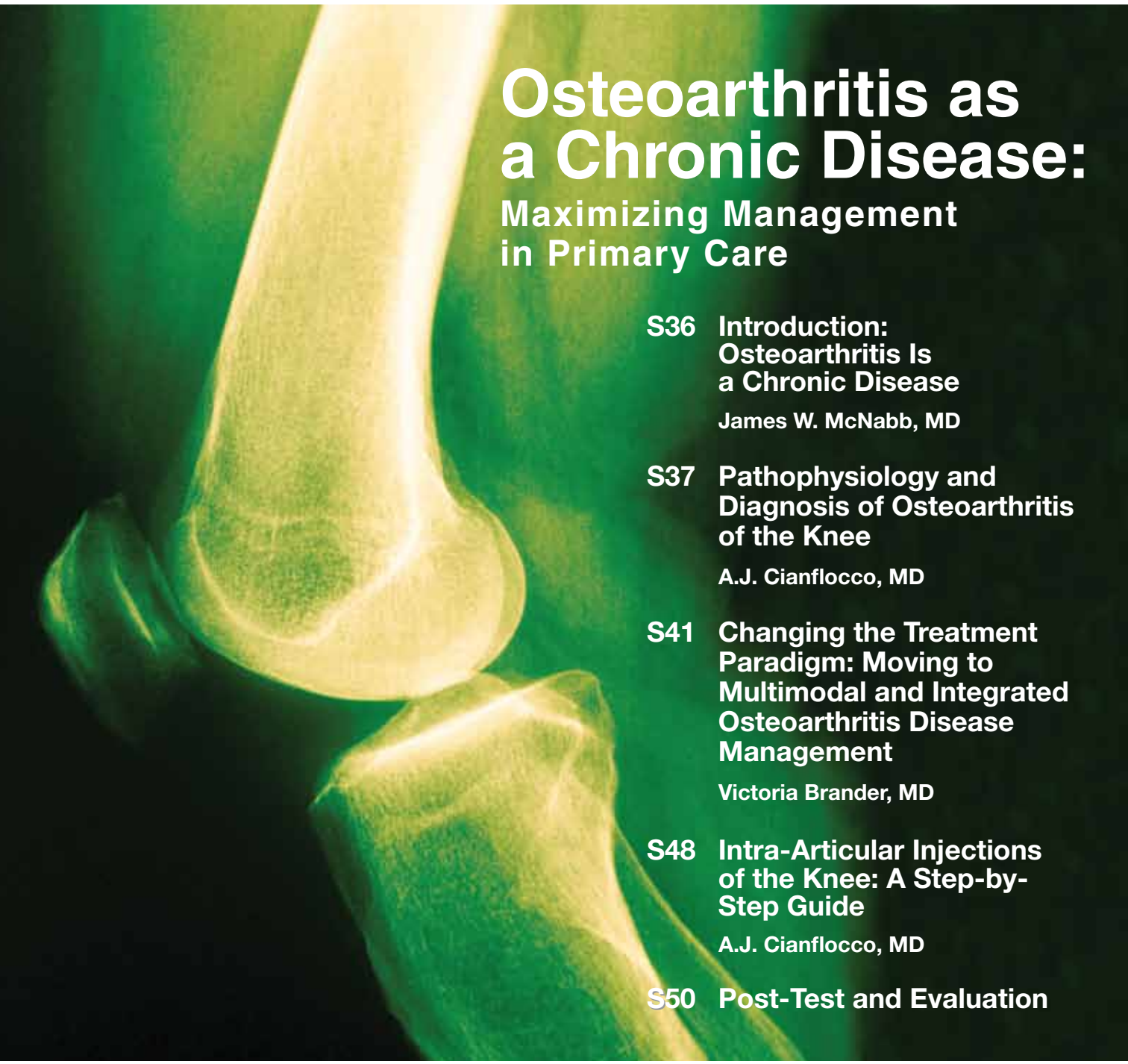

Osteoarthritis as a Chronic Disease:
Maximizing Management in Primary Care

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OVERVIEW

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide. In the United States alone, it is believed that approximately 27 million people are affected by this degenerative condition. Many factors are known to increase the risk of developing OA, including heredity, obesity, joint or nerve injury, repeated overuse of certain joints, lack of physical activity, and aging. Treatment goals for patients with OA of the knee include reduction of pain, improvement in joint mobility, improved quality of life, and limited functional impairment while avoiding drug toxicity.

Treatment needs to be individualized according to the stage of the disease, the tolerability of the patient, comorbidities involved, and response to treatment. Additionally, the complexities of the underlying pathophysiological possibilities mean that every individual who presents with OA of the knee is unique.

Primary care clinicians can and should have a greater role in the diagnosis and treatment of OA of the knee. Clinicians are charged with being a diagnostician, a referral center, and, more often than not, a caregiver to patients with OA of the knee. There are many barriers to patients being managed by a rheumatologist and/or an orthopedic surgeon, which include access to the specialist as well as cost issues. It is important for clinicians to be educated on the latest advances in the pathogenesis and underlying phenotypes of OA in order to better diagnose and classify the disease, and subsequently treat patients with OA of the knee appropriately with a maximum improvement in functionality, while minimizing pain and drug toxicities. In addition, clinicians provide care for patients' comorbidities, so an understanding of OA of the knee would minimize potential roadblocks in patients' overall care.

LEARNING OBJECTIVES

Upon completing this activity, participants should be better able to

- Use an understanding of the pathophysiological mechanisms of OA of the knee to tailor therapy for disease modification and pain management
- Customize a multimodal treatment plan to maximize mobility based on stage of disease, comorbidities, drug tolerability and interactions, and response to treatment
- Identify patients who may benefit from intra-articular injections of the knee
- Describe the benefits and risks associated with the administration of intra-articular injections of the knee in the primary care setting

TARGET AUDIENCE

This activity is targeted to any primary care provider who treats patients with osteoarthritis of the knee.

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Introduction: Osteoarthritis Is a Chronic Disease

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Osteoarthritis (OA) is a serious disease characterized by chronic arthropathy, disruption of joint cartilage, osteophyte formation, and synovial fluid abnormalities.[1] OA affects an estimated 27 million Americans, making it the most common of more than 100 types of arthritis. The prevalence of OA increases with age, and currently 34% of individuals older than 65 years have OA.[2] Until recently, most OA in younger patients has been attributable to joint trauma. However, OA is also a common comorbidity in people with obesity, cardiovascular disease, and impaired glucose metabolism[3]; while the prevalence of these chronic conditions reaches epidemic proportions, particularly for obesity and diabetes, the number of OA diagnoses in younger individuals is rising.

The economic impact of OA is considerable. Some estimates bring the costs for OA-related healthcare to $185.5 billion annually in the United States.[4] OA that affects weight-bearing joints has substantial clinical impact. Approximately 1 in 100 adults has moderate-to-severe knee OA.[3] Knee OA is one of the top 5 causes of disability among noninstitutionalized Americans. More than 1 in 10 patients with knee OA need help with personal care, and 25% require assistance with routine activities.[5] OA-related disability affects a patient's ability and willingness to be physically active. Because exercise is a foundational part of managing OA as well as for managing obesity, cardiovascular disease, and impaired glucose metabolism, the pain of knee OA is an important and treatable barrier in adherence to recommended therapy.

An estimated 80% of individuals with OA visit their primary care physician at least once a year.[6] We hope that this supplement empowers family physicians to provide proper care for their patients with OA of the knee through the entire disease spectrum—from initial diagnosis to surgical intervention. Many primary care physicians refer their patients who need intra-articular injections to subspecialists. Others are comfortable administering intra-articular corticosteroids, but hesitate to provide hyaluronate injections. Such referrals may be unnecessary, leading to fragmentation of care and undermining the patient-centered medical home.

The first article in this supplement by Dr. Alfred Cianflocco provides an overview of the pathophysiology of knee OA as a whole joint disease and reviews its diagnosis. The article by Dr. Victoria Brander discusses individualized multimodal treatment of knee OA with an emphasis on treating individuals with comorbidities. Finally, Dr. Cianflocco presents a step-by-step guide to performing knee intra-articular injections.

We sincerely hope this supplement serves as a call to action to screen patients for knee OA and helps you become comfortable with all aspects of providing multimodal therapy. ■

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Pathophysiology and Diagnosis of Osteoarthritis of the Knee

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Introduction

Osteoarthritis (OA), once considered a consequence of aging, is now understood to be a progressive disease that results from complex interactions of multiple physical and biochemical factors.[1,2] OA of the knee is a common comorbidity in patients with other serious chronic medical conditions, such as cardiovascular disease, diabetes, and obesity. Because OA knee pain limits physical activity, consequences of untreated knee pain can be far reaching since physical activity is such a major component of therapy for OA and other chronic medical conditions. Recognizing that OA involves more joint structures than the articular cartilage is important for diagnosing and individualizing patient treatment.

Pathophysiology

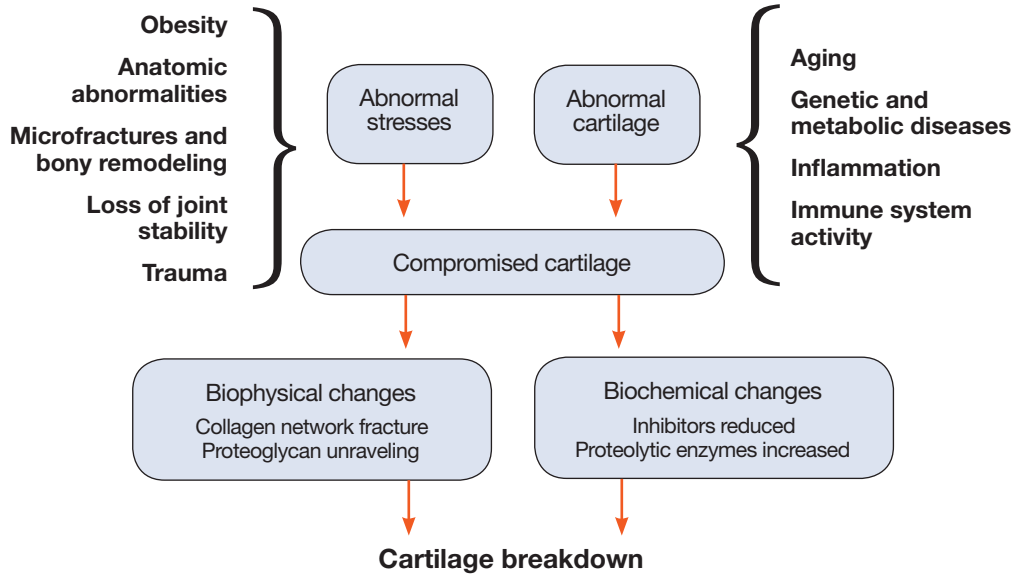
As shown in **FIGURE 1,** excess weight, structural abnormalities, microfractures, loss of joint stability, and joint trauma cause abnormal mechanical stresses on the knee joint.[1] Chondrocytes serve as mechanical stress sensors that trigger elaboration of inflammatory mediators and proteolytic enzymes in response to these abnormal mechanical stresses.[2] These stresses lead to compromised cartilage. Alternatively, abnormal or compromised cartilage may also be the result of aging, genetics, or metabolic disorders. Abnormal stresses on the joint and abnormal cartilage, alone or combined, initiate a cascade of proliferative and inflammatory processes that lead to further damage, and a self-perpetuating and progressive cycle of joint disease ensues.[1]

At first, articular cartilage may be the primary injury site, but eventually all joint structures—bone, synovium, muscle, capsule, ligaments, and meniscal cartilage—become involved[2,3] (**FIGURE 2**). Cartilage degradation generally can be explained by insufficient reparative and anabolic response to increased proteolytic and destructive activity within the joint.[2] Fueled by proinflammatory mediators,[2] changes occur in the synovium and chondrocyte metabolism is altered.[2,4] Elasticity and viscosity of synovial fluid changes[5] as hyaluronic acid concentration decreases. Weight-bearing activity becomes painful, often limiting physical activity.

Traditional risk factors of knee OA include obesity[4] (body mass index ≥30 kg/m^2), African American heritage,[6] and age.[7] Genetics play a role, as do joint injuries and manual labor professions.[6] Women are more likely to develop knee OA than men and the incidence in women increases dramatically at menopause, suggesting a result of estrogen deficiency.[8]

OA is highly prevalent in patients with cardiovascular risk factors associated with the metabolic syndrome—abdominal obesity, high triglyceride levels, low high-density lipoprotein cholesterol levels, hypertension, and hyperglycemia. The association of OA with cardiovascular factors is particularly striking in younger individuals (**TABLE 1**). In the United States, 65% of adults younger than age 65 who have OA also have at least 3 cardiovascular risk factors compared with only 21% of that age group without OA.[9] This relationship is not surprising given the similarities in underlying inflammatory pathophysiologies with OA, cardiovascular disease, and hyperglycemia. Moreover, the relationship suggests that clinicians who see patients at high risk of cardiovascular disease should consider asking them about knee pain.

FIGURE 1 **Pathogenic factors in osteoarthritis**



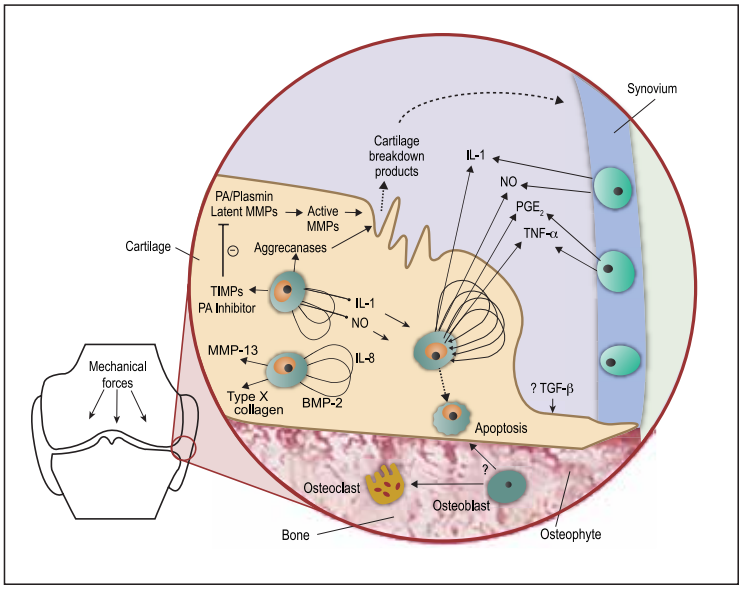
Adapted from: Mandelbaum B. *Orthopedics*. 2005.[1]

Diagnosis

History and physical examination are the most sensitive diagnostic tools for patients with knee pain. Initial complaints typically involve pain with weight-bearing activities, morning stiffness lasting usually less than 30 minutes, and episodes of knee buckling.[10] Because knee pain in OA is frequently associated with articulation of the patellofemoral joint, activities such as stair climbing that involve bending the knee are likely to cause pain as well as ambulating on a level surface. Physical examination should include assessment of alignment, gait, and core stability. Varus (bowlegged) and valgus (knock-kneed) alignment are predictive of worsening radiographic disease.[10] Limping and slow gait are indicative of knee pain; to rule out referred pain from the hip, an examination of the hip joint and range of motion (ROM) are necessary.[10] The painful knee joint should be examined for the presence of effusion, tenderness, ROM, and laxity.

TABLE 2 lists conditions that should be considered as part of a differential diagnosis of knee OA. Features that can distinguish these conditions from OA are noted as well. Laboratory tests may be necessary in cases of suspected inflammatory arthritis, gout or pseudogout, and infection, but generally are not necessary for OA diagnosis.[10] Experimental use of both molecular and imaging biomarkers has provided new insights into the pathophysiology of OA.[2] These tools, although promising, are not yet ready for clinical application.

FIGURE 2 **Pathogenic changes leading to whole organ disease[15]**



BMP, bone morphogenetic protein; IL, interleukin; MMP, matrix metalloproteinase; NO, nitric oxide; PA, plasminogen activator; PG, prostaglandin; TGF, transforming growth factor; TIMP, tissue inhibitor of MMP; TNF, tumor necrosis factor.

Reprinted from: Abramson SB, et al. *Arthritis Res Ther*. 2009.[15]

TABLE 1 **Prevalence of the metabolic syndrome is increased among patients with OA[9]**

Age	OA	No OA	*P* value
18-64 years	65%	21%	<.001
≥65 years	54%	45%	<.045

N=7714.

OA, osteoarthritis.

The metabolic syndrome is characterized by ≥3 of the following conditions: abdominal obesity, high triglyceride levels, low high-density lipoprotein cholesterol levels, hypertension, and hyperglycemia.

TABLE 2 **Features that distinguish various causes of chronic knee pain from knee OA[a,10,14]**

Conditions	Features according to history	Features on physical examination	Laboratory and radiographic features
Chronic inflammatory arthritis, including rheumatoid arthritis	Prominent morning stiffness, other joints affected (symmetrically)	Other joints swollen or tender, hand deformities	Increased erythrocyte sedimentation rate; inflammatory synovial fluid, erosions on radiographs
Gout or pseudogout (chondrocalcinosis, CPPD)	Other joints affected, especially great toe (for gout), wrists, or shoulders (pseudogout)	Other joints swollen or tender	Inflammatory synovial fluid containing crystals, radiographs may show chondrocalcific lime (CPPD)
Hip arthritis	Groin, trochanteric, or buttock pain, or only anterior knee pain in many cases	Pain with hip flexion and internal rotation; Trendelenburg lurch tenderness	Abnormal hip radiograph
Chondromalacia patella	Onset at relatively young age; predominance of anterior knee symptoms (pain with kneeling, stairs, squatting)	Tenderness only over patellofemoral joint, pain with patellar pressure (inhibition, grind tests)	Normal radiograph or mild patellar irregularity on sunrise view
Anserine bursitis	Anteromedial knee pain	Tenderness distal to knee over medial tibia	Normal radiograph
Trochanteric bursitis	Lateral hip pain, especially at night	Tenderness in region of lateral hip	Normal radiograph
Iliotibial band syndrome	Lateral thigh pain, extending to lateral knee	Tenderness and tightness of the iliotibial band[b]	Normal radiograph
Joint tumors	Nocturnal or continuous pain		Bloody synovial fluid and possibility of abnormality on X-ray
Meniscal tear	Prominent mechanical symptoms (eg, locking or buckling) and effusion	Tenderness over joint line; positive results on McMurray test[c]	Meniscal tear on MRI, radiographs normal

CPPD, calcium pyrophosphate dihydrate; MRI, magnetic resonance imaging; OA, osteoarthritis.

[a]Pain is considered chronic if it lasts ≥6 weeks.

[b]Tenderness of the iliotibial band is usually lateral to the knee over the insertion site of the iliotibial band in the fibular head or superior to the insertion site, where it courses over the lateral femoral condyle.

[c]No physical examination maneuver for meniscal tears has both high sensitivity and specificity. Tenderness at the joint line has a sensitivity of 79% and a specificity of 15%, whereas a McMurray test has a sensitivity of 53% and a specificity of 59%. Results of a McMurray test are positive if a click is palpable or pain is elicited over the medial or lateral tibiofemoral joint line during flexion and extension of the knee during varus (medial tear) or valgus (lateral tear) stress. These data are derived from studies of acute tears, and diagnostic data are not available for chronic tears.

Adapted from: Felson DT. *N Engl J Med*. 2006.[10]

Weight-bearing radiographs are an important diagnostic test for confirming a diagnosis of knee OA (**FIGURE 3**).[11] Although magnetic resonance imaging (MRI) can detect changes in the articular cartilage earlier than radiographs, MRI generally has no role in diagnosing knee OA.[2] Patients who are likely to have a meniscal tear or mechanical symptoms are candidates for MRI.[10] However, to confirm an OA diagnosis, bilateral weight-bearing posteroanterior radio-

FIGURE 3 **Comparison of weight-bearing vs nonweight-bearing x-rays**

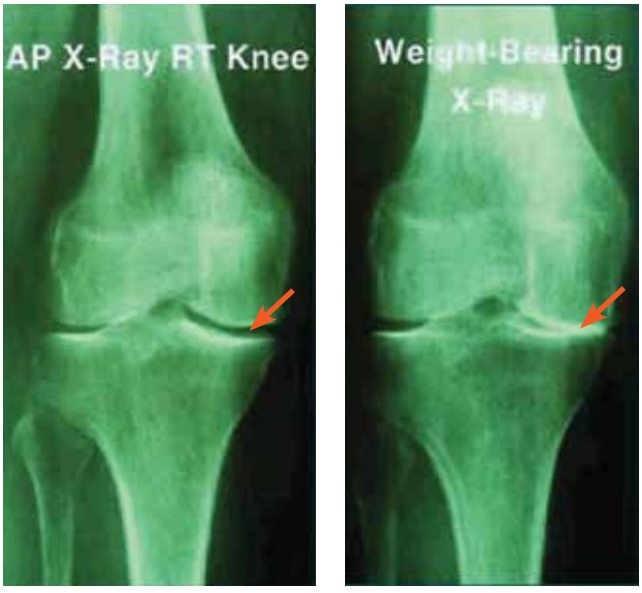


PHOTO COURTESY VICTORIA BRANDER, MD

Left image shows an anterior posterior (AP) view of the knee with the patient in a supine position. The right image shows the same AP view of the knee X-rayed with the patient standing. The arrows indicate the different appearance of joint spacing in the 2 positions.

graphs should be taken at 0° and 45° of flexion. In addition, a nonweight-bearing lateral radiograph should be taken at 30° flexion as well as a Merchant/sunrise radiograph. **FIGURE 3** shows the difference between supine and weight-bearing X-rays in a patient with knee OA. Weight-bearing views, in particular the weight-bearing views taken at 45° of flexion, can help identify joint space narrowing; the flexion view visualizes a different weight-bearing area of the femur and tibia. The lateral and Merchant views visualize the patellofemoral joint and the tibiofemoral joint as well. Radiographic findings of OA of the knee include joint space loss, subchondral sclerosis, subchondral cyst formation, osteophyte formation, and flattening of the femoral condyles.[12,13]

Once a diagnosis of OA is confirmed, individualized multimodal treatment is required to reduce pain, improve joint mobility, and limit functional impairment. It is important to remember that the OA radiographic severity does not always correlate with a patient's pain. The patient's pain and its impact on mobility and quality of life should be the drivers of treatment and pain management. ■

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Changing the Treatment Paradigm: Moving to Multimodal and Integrated Osteoarthritis Disease Management

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A perfect storm is brewing—an exponentially increasing prevalence of osteoarthritis (OA), an aging baby boomer population, and an epidemic of obesity and chronic disease. By 2020, some statistics forecast the number of people with OA will have doubled.[1] National Health and Nutrition Education Survey III data report that OA is highly prevalent in adults with abdominal obesity, high triglyceride levels, low high-density lipoprotein cholesterol levels, hypertension, or hyperglycemia.[2] Moreover, individuals with OA are more than twice as likely to have metabolic syndrome, defined as at least 3 of those cardiovascular risk factors. While 25.5% of the overall population surveyed met the criteria for metabolic syndrome, the prevalence was 59% ($P<.001$) among people with OA.[2]

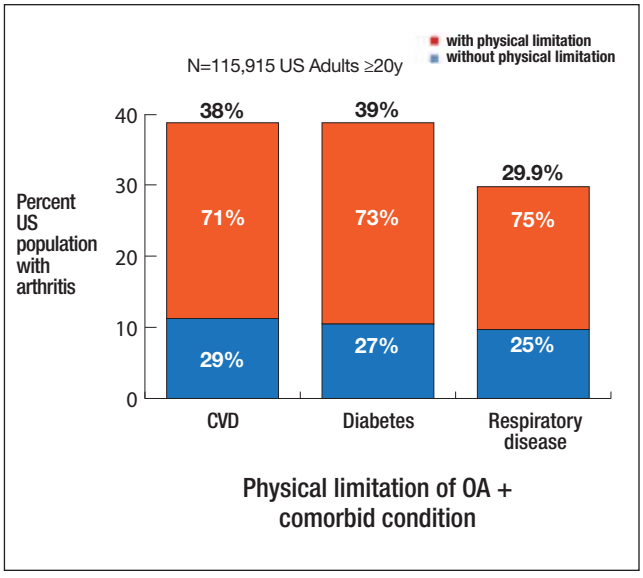
Why is this relationship important? Not only is exercise the cornerstone of arthritis treatment, physical activity is a critical strategy for long-term disease management. So when OA is superimposed on chronic illnesses, mobility suffers. More than 70% of patients with OA and comorbid diabetes, cardiovascular disease, or respiratory disease report limited activity as a consequence of their arthritis pain (**FIGURE 1**).[3] Their sedentary lifestyle is, literally, a killer. Patients with OA are at a higher risk of all-cause mortality, and the greater the severity of walking disability, the higher the mortality risk ($P<.001$ for trend).[4] Therefore, primary care clinicians need to view treatment for arthritic knee and hip pain as essential in improving patients' quality of life, and all the more critical in patients with comorbid chronic illnesses.

Multimodal Disease Management for OA

Although there are a variety of options to reduce OA pain and disability, despite clinicians' best intentions, the unfortunate reality is that treating the painful knee is often relegated to the last few minutes of a primary care visit and consists of an anti-inflammatory prescription and waiting for knee replacement.[1] There are a plethora of treatment options. OA clinical trials are challenging to both perform and interpret because symptoms wax and wane and there tends to be a high placebo effect. No single therapy has shown dramatic results; for that reason, there is no specific "right" place to start treatment. Although treatment algorithms usually recommend "stepwise" management (eg, "first try acetaminophen, then try NSAIDS," etc), this antiquated approach has been fairly ineffective at reducing pain, lessening disability, or improving patients' satisfaction with care. One market research study suggested that nearly three-quarters of patients who received traditional OA care of the knee were dissatisfied with their treatment.

Instead, let's rethink how we deliver OA care, approaching treatment using the disease-management strategies that have been effective in other chronic conditions. Primary care physicians should take a proactive approach to reduce patients' pain and improve their function using multiple modalities, both nonpharmacological and pharmacological (**FIGURE 2**). Whatever treatment plan is agreed on with the patient, regular follow-up visits are essential to ensure pain relief is adequate and no adverse effects have developed, and to reinforce adherence with the exercise treatment regimen.

FIGURE 1 **Arthritis limits physical activity in >70% of individuals with CVD, diabetes, and respiratory disease[3]**



CVD, cardiovascular disease; OA, osteoarthritis.

Nonpharmacological Interventions

A range of nonpharmacological treatment options are available that both improve joint function as well as reduce pain (**TABLE 1**). Treating pain early builds patients' trust in the clinician's judgment and demonstrates that steps can be taken to improve patients' lives. In clinical practice, treatment with an intervention (such as a steroid and/or hyaluronate injection) that rapidly reduces pain may be the first treatment choice. Once pain is controlled, the patient can enroll in a physical therapy program to enforce a regular exercise regimen. The early pain relief builds the patient's trust in the provider's judgment; coupled with physical therapy, it reduces the patient's anxiety about physical activity and associates exercise with feelings of improvement. This combination motivates patients to adhere to their treatment regimens and increases confidence in their ability to improve their health. At subsequent visits, patients may be more receptive to discussions of weight loss, self-management techniques, or other interventions that reduce pain and improve function. Patients may be surprised to find that for every pound of weight they lose, there is a reduction of 4 pounds of load on their painful knee.[5] Telephone follow-up can help to sustain that self-efficacy. One randomized control trial involving 439 patients with knee OA found that monthly telephone check-ins by a layperson to remind patients of their regimen had the effect of improving their joint pain and physical function for up to 1 year.[6]

Exercise

Exercise is the single most important strategy in reducing the disability from OA. Every patient with OA should be prescribed an exercise regimen, and numerous studies have confirmed the benefits of exercise. Quadriceps strength training, for example, was shown to reduce disease progression in a study of middle-aged women.[7,8] Patients with OA have reduced cardiovascular endurance compared with their nonarthritic peers.[9] Exercise, both aerobic and strengthening, improves pain, reduces disability, and improves cardiovascular fitness in arthritis.[9] Quadriceps and gluteal muscle atrophy is common in knee OA, leading to pain and difficulties with common activities, such as getting up from a chair or climbing stairs. Focused exercise programs can reverse these functional limitations.[10] Several investigators have reported improvements in pain and function with supervised exercise programs and physical therapy.[11-14] Aggressive strength exercises appear to be more effective than the "gentle isometrics" traditionally prescribed.[7] However, in the absence of sustained exercise or "booster" sessions, the benefits of exercise diminish over time; therefore, regular reinforcement by the treating physician is necessary to ensure adherence.[15]

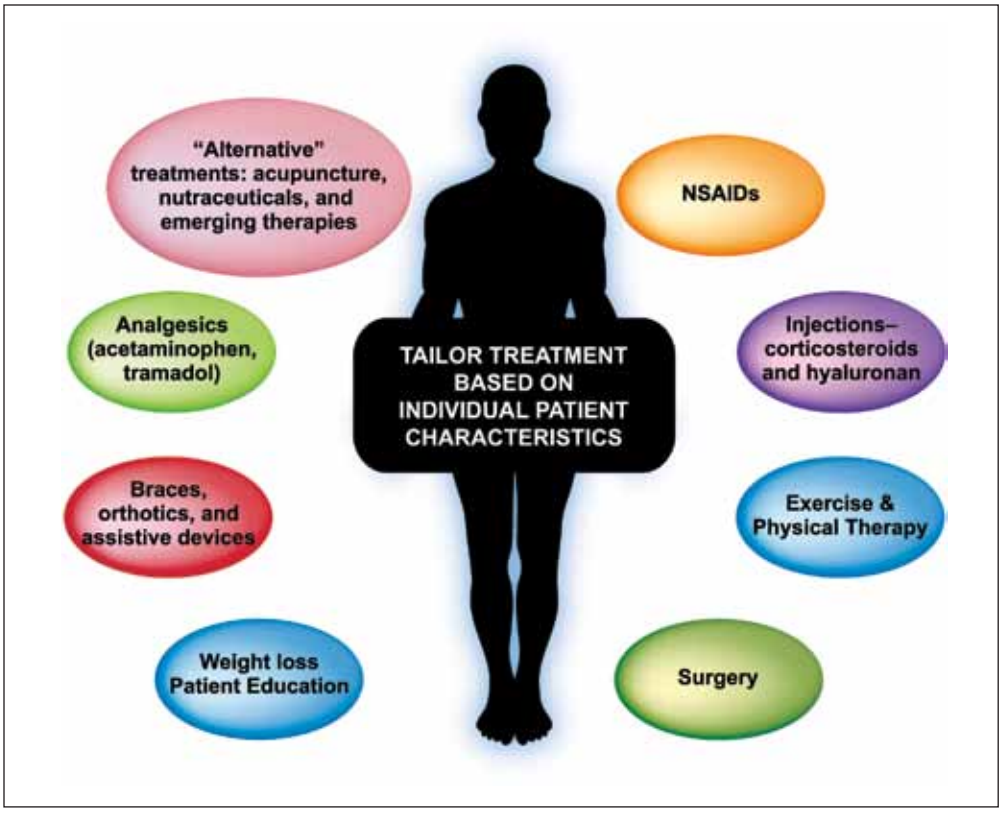
Supports and braces

When OA of the knee progresses, varus and valgus malalignments worsen. Foot pronation deformities (including flat feet) are common in patients with valgus knees. Arch support with a medial post can reduce lateral knee stress and may help with pain. Similarly, lateral wedges can be prescribed for patients with varus deformities.[16] A recent study found that lateral wedge insoles may be an alternative to valgus bracing.[17] Bracing has been shown to provide greater improvement in Western Ontario MacMasters (WOMAC) scores than a neoprene sleeve alone.[18] Active patients with varus or valgus knees might benefit from knee unloader braces.[19] These braces can be difficult to fit for obese or short patients, and are expensive, although they are covered by Medicare and most insurance plans. Patients should be selected carefully. If patients have a unilateral valgus deformity, the physician should measure the patient's leg length. Unilateral valgus knee can be an adaptation to a long leg; in this situation, a lift in the opposite shoe might help.

Other strategies

Chronic painful joint stiffness can be reduced with the application of heat packs, and immersion in warm water or wax baths can be effective. For some patients, application of ice packs or ice massage is also effective. There is no "right or wrong" hot or cold modality—patients should choose whichever helps them feel better. The use of a transcutaneous electrical nerve stimulation (TENS) unit may help reduce some

FIGURE 2 **Multimodal therapy for treatment of knee OA[57]**



forms of chronic pain; a recent meta-analysis found evidence of efficacy in OA to be inconclusive.[20] The author finds the TENS unit somewhat useful for managing spinal stenosis pain but not very useful for pain from hip or knee arthritis. Several studies of acupuncture have demonstrated short-term pain relief in arthritis.[21] However, issues with placebo effect and standardization of control groups cloud interpretation of these studies. The latest meta-analysis of acupuncture in OA treatment of the knee included results from 11 randomized control trials and was inconclusive.[21]

Benefits and Risks of Pharmacological Therapy

For most patients, some form of pharmacological intervention is needed for acute flares of pain. A growing body of evidence suggests that even over-the-counter (OTC) analgesics are far from benign agents, particularly in individuals with other chronic conditions. Individualizing the choice of pain medication is an important consideration in developing a multimodal regimen. **TABLE 2** lists the considerations associated with treatment options.

Acetaminophen is effective in providing acute pain relief for patients with mild knee OA.[22,23] Caution should be used in prescribing acetaminophen for patients at risk of hepatotoxicity, and all patients should be advised not to exceed 3 g per day. Education is important—patients may not be aware that OTC medications, such as cold or combination pain medications, contain acetaminophen. To reduce the risk of inadvertently exceeding the maximum recommended dose, the US Food and Drug Administration (FDA) asked manufacturers of prescription acetaminophen products to limit the maximum amount of acetaminophen in these products to 325 mg or less per unit in January 2011.[24] However, this was a request rather than a requirement and higher doses remain available. A recent placebo-controlled crossover study demonstrated blood pressure elevations in 33 patients with coronary artery disease during treatment with 3 g acetaminophen per day.[25]

Several topical anti-inflammatory formulations are available for OA treatment. The Osteoarthritis Research Society International (OARSI) recommends topical diclofenac as adjunctive or alternative therapy.[23] Topical administration is associated with low systemic exposure. A single head-to-head trial found the efficacy of topical diclofenac to be similar with that of oral NSAIDs.[26] Most patients find that it takes a full week of use to achieve clinical benefit. In the author's experience, topical anti-inflammatory treatments are more likely to be effective in smaller rather than larger joints.

Capsaicin cream is another topical alternative recommended by OARSI.[23] Efficacy, however, has not been well established. Application of this chili pepper extract is associated with a burning sensation during the first several days of use that some patients cannot tolerate.[23] Patients should be counseled to wash their hands immediately after applying capsaicin to avoid getting the product in their eyes.

Although there is a large body of anecdotal evidence supporting their use for OA, the effectiveness of glucosamine and chondroitin has not been confirmed by large, rigorous trials.[27-29] A double-blind, randomized placebo-controlled trial sponsored by the National Institutes of Health was conducted to evaluate the efficacy of these compounds in 1583 patients with knee OA. Glucosamine 1500 mg and

TABLE 1 **Nonpharmacological treatment options**

- Patient education—disease self-management
- Telephone follow-up
- Self-directed and community exercise
- Physical therapy
- Weight reduction
- Thermal modalities
- Acupuncture
- Manual therapies—massage, manipulation
- Electrical stimulation—TENS, functional electrical stimulation
- Foot orthotics—including medial or lateral wedges
- Knee bracing
- Walking aids—cane, walker, etc

TENS, transcutaneous electrical nerve stimulation.

chondroitin 1200 mg were compared alone or in combination for a 2-year period. No significant benefit was observed with nutraceutical use versus placebo in the overall group of patients with OA of the knee.[27,30] A retrospective analysis of the same data suggested moderate pain relief was found in patients with moderate-to-severe OA pain.[30] Moreover, meta-analysis of data from 10 trials involving 3803 patients with knee or hip OA revealed no treatment benefit with glucosamine, chondroitin, or their combination versus placebo.[31] Studies have been unable to confirm any "cartilage building" or disease-modifying effects of these agents.[29] Glucosamine and chondroitin can increase bleeding in patients taking warfarin or patients with bleeding,[32] and there is concern that glucosamine can increase insulin resistance.[33]

Oral NSAIDs such as ibuprofen are associated with superior pain relief for acute moderate-to-severe pain compared with acetaminophen.[34,35] When prescribing these agents for individuals with comorbid conditions, several potential adverse effects should be considered. In general, NSAIDS are associated with substantial cardiovascular and cerebrovascular risk. A meta-analysis of 31 studies found that the risk of stroke is greatest with ibuprofen and the risk of myocardial infarction is greatest with cyclooxygenase-2 (COX-2) inhibitors.[36] Caution is advised when prescribing NSAIDs to patients at risk of upper gastrointestinal (GI) bleeding. Approximately 16,500 deaths are related to NSAIDS each year.[37] In elderly patients, between 20% and 30% of peptic ulcer hospitalizations and deaths are related to NSAID use.[22] These drugs are also associated with a risk of renal toxicity.[23]

Opioids can significantly reduce pain and modestly improve function in patients with OA.[38,39] However, a high rate of adverse effects, including nausea, constipation, dizziness, and somnolence, limits their use.[40,41] Opioids also carry a risk of dependence, abuse, and diversion.

Tramadol is a centrally acting, weak μ-opioid agonist and a norepinephrine and serotonin reuptake inhibitor.[42,43] Several clinical trials have documented improvements in pain, function, and well-being in cases treated with tramadol.[44] Because of its efficacy and low adverse effect profile, tramadol may be prescribed as a first-line analgesic for OA pain.

Intra-articular Injections

Intra-articular injections are not difficult to perform and have limited systemic risk when used appropriately, offering

TABLE 2 **Risks of multimodal treatment options**

Treatment	Risk assessment needed
Acetaminophen	Hepatotoxicity with high-dose acetaminophen or already taking combination pain medications[23,24,58]; coronary artery disease[25]
NSAIDs (including COX-2 inhibitors)	Comorbid cardiovascular and cerebrovascular disease[36,59];at risk of GI bleeding[37,60]; kidney disease[61]; anticoagulant interaction; edema; diabetes; advanced age; asthma
Tramadol	Constipation; heightened seizure risk on SSRIs; epilepsy; abuse potential
Opioids	Abuse or diversion; constipation; cognitive impairments
Steroid injections	Diabetes[46]; hypertension[48]; edema[48]; osteoporosis; endocrine disorders; infections
Hyaluronate injections	Avian protein allergy[62] Contraindicated in presence of infection; inflammatory arthritis (RA, gout, CPPD deposition disease)
Joint replacement	Young age; surgical risk; morbid obesity; thromboembolic disease; previous joint infection

COX, cyclooxygenase; CPPD, calcium pyrophosphate dihydrate; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SSRIs, selective serotonin-reuptake inhibitors.

the promise of local treatment for local disease. Corticosteroids are potent anti-inflammatory agents and their intra-articular administration provides good short-term pain relief (2-4 weeks).[44] Pain relief is typically rapid. Injections can be administered at intervals to maintain efficacy. The most efficacious and well-tolerated interval between injections has not been established. One study showed that injections administered every 3 months provided effective pain relief for 1 year. Efficacy diminished in patients who continued treatment for a second year.[23,45]

Systemic and local adverse events limit the use of injectable steroids. Local soft-tissue reactions can include skin depigmentation, subcutaneous atrophy, and muscle or tendon ruptures.[46] Systemic complications include elevations of blood sugar up to 2 weeks after the injection in patients with diabetes; therefore, use with caution in these patients.[47,48] Steroid injections given on a regular basis are associated with significant systemic risk, including adrenal axis suppression, iatrogenic Cushing's syndrome, menstrual cycle irregularities, osteoporosis, and blood pressure elevations. Because steroids suppress synthesis of collagen and proteoglycans, there is concern that intra-articular steroids might cause articular cartilage deterioration. This has not been confirmed in human trials. Last, occasionally patients will experience transient facial flushing lasting 1 to 2 days that resolves spontaneously.[48]

Hyaluronate (HA) is a natural component of synovial fluid. Intra-articular injections of HA are recommended for reducing pain and improving function in patients with knee OA.[49] Unlike corticosteroids, pain relief begins about a month after the injection and lasts for more than 6 months.[50] The exact mechanism of action is not entirely known; however, experimental evidence suggests that HA injections may work through both mechanical and metabolic effects. Injections have been shown to stimulate endogenous HA production, chondrocyte growth, and synthesis of extracellular matrix proteins. HA has anti-inflammatory effects and can inhibit metalloproteinase activity.[51] A 2006 Cochrane review concluded that HA injections modestly reduce pain scores in patients with OA of the knee, with the largest benefit occurring within 5 to 13 weeks.[49] Many clinicians think that HA injections can delay the decision for total knee-replacement surgery, although the published evidence for this assumption is limited.[52,53] Intra-articular administration of HA is well tolerated.

Patients occasionally experience transient joint pain after the injection. In rare cases, within 12 hours of an injection, patients can experience a profound inflammatory reaction that causes significant joint pain and swelling. This should be treated urgently with joint aspiration and corticosteroid injection.[51] Hyaluronan injections should be used cautiously in patients with a history of gout or chondrocalcinosis because the injections could prompt a flare. All intra-articular injections should be performed cautiously in patients taking anticoagulants. They are contraindicated in the presence of an active infection.[54] In the author's opinion, injections into a previously septic joint are not recommended. Formulations derived from avian sources should not be used in patients with allergies to avian proteins.[54]

Surgery

When pain and increasing functional loss begin impairing a patient's quality of life, referral for joint arthroplasty is appropriate. Arthroscopic surgery is not indicated for most patients with OA and should be considered only when there is an abrupt, new mechanical symptom, such as locking and effusion, in a patient with very stable and mild degenerative disease.[55] Hip and knee replacements are remarkable surgeries, dramatically reducing pain and restoring function. Most patients are so happy with surgery results that, in retrospect, they feel they waited too long to consider it. Patients should be referred to an orthopedist before they incur extensive irreversible disability. Low preoperative functional level predicts worse outcome after surgery.[56]

All patients should undergo a comprehensive rehabilitation program preoperatively as a way to facilitate their postoperative recovery. This should include physical therapy, a customized home exercise program, and aggressive pain management. Preoperative pain is a strong predictor of poor outcomes after joint replacement surgery.[55] Less invasive surgical techniques, better fitting implants, regional anesthesia, and aggressive postoperative physical therapy protocols have markedly improved patient safety, outcome, and satisfaction.

CASE STUDIES: Individualizing Treatment

CASE 1 ▶ M.J. is a 64-year-old woman who presents with right knee swelling and pain for a month. She has had previous similar episodes. She is obese but has no other comorbidities. She has tried over-the-counter anti-inflammatories intermittently. Because of the intermittent flares of pain and some mild baseline chronic pain, she is not exercising.

On physical examination, she is found to have atrophy of the quadriceps and gluteal muscles. Her right knee is tender and effusion is evident. Prior standing knee radiographs have shown medial joint space narrowing and intra-articular calcifications, consistent with chondrocalcinosis.

In addition to pain relief, the goal of therapy for M.J. is to improve her mobility. Long-term goals are weight reduction and improved strength. M.J. is an excellent candidate for an intra-articular corticosteroid injection to reduce inflammation from the chondrocalcinosis flare. She feels relief soon after the injection. After considering the renal, GI, and cardiovascular risks, you

instruct her about taking full doses of an NSAID to reduce pain during flares. You explain that NSAIDs are more effective than other analgesics because they reduce the inflammation causing the pain in calcium pyrophosphate disease flares.

At her follow-up visit, M.J. reports that her pain has improved considerably. Now that she is feeling better, you provide M.J. with access to education about disease self-management and weight loss. You refer her for physical therapy and customized exercise.

CASE 2 ▶ B.L. is a 45-year-old man who presents with chronic mild-to-moderate knee pain that limits his golf playing. He is taking an antihypertensive agent for his hypertension and metformin and a sulfonylurea for his type 2 diabetes. He does not want to take any more medication. He has already tried over-the-counter ibuprofen and acetaminophen for his knee pain.

On physical examination, he stands with mild valgus deformity at the knees. He has flat feet and no effusion. He has mild quadriceps atrophy. He is unable to maintain a single leg stance, with his hip dropping into the Trendelenburg position. Standing radiographs show lateral compartment joint space narrowing particularly in the PA flexion film.

The treatment goals for B.L. are to relieve pain, restore limb alignment and strength, and keep him active. Because of his comorbid hypertension and diabetes, B.L. is not an ideal candidate for NSAIDs. His pain is chronic and there is no evidence of inflammation. That fact, in concert with his history of diabetes, suggests steroid injection is not the best choice. You administer intra-articular HA and prescribe tramadol to manage his pain flares. You also refer him to be fitted for foot orthotics with a medial wedge as well as a knee unloader brace, which he will use during golf, and refer him for customized exercises in physical therapy. ■

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Intra-Articular Injections of the Knee: A Step-by-Step Guide

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Although some training is required, intra-articular injections are no longer considered an orthopedic subspecialty procedure, and there are a number of benefits to incorporating these injections into your practice. Many patients appreciate their primary care clinician making available services that traditionally required a referral to a specialist. Patients also avoid treatment delays.

Here is a step-by-step guide to familiarize you with the technique.

STEP 1 Selecting an injection approach

Common approaches for injecting the knee include the following[1]:

- Anterolateral (flexed knee)
- Anteromedial (flexed knee)
- Superolateral/lateral suprapatellar (straight knee)
- Superomedial/medial suprapatellar (straight knee)
- Lateral mid-patellar
- Medial mid-patellar.

One study found that the accuracy of the first attempt at needle placement was highest for lateral mid-patellar (93%) compared with anteromedial (75%) and anterolateral (71%) approaches (superolateral approach not done).[1]

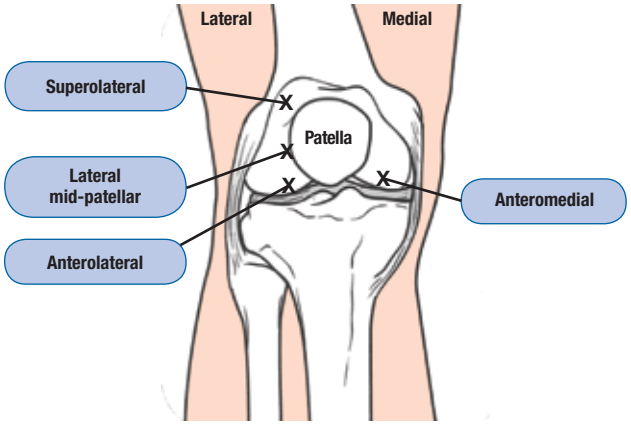


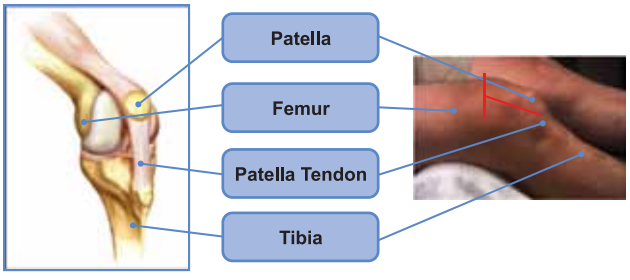
IMAGE COURTESY OF XME, LLC

STEP 2 Identify and mark the injection site[2]

For superolateral approach:

- Palpate superolateral and lateral edges of patella with patient supine and leg straight
- Mark where lines intersect as in diagram.

If the patient cannot completely extend the knee, placement of a rolled towel to support the knee will help provide the patient comfort and minimize muscle spasm, improving the likelihood of a successful and comfortable injection.



RENDERING COURTESY OF XME, LLC. PHOTO COURTESY OF McNABB JW. http://5minuteconsult.com/videos/McJSTI01KneeJointAspInj.html

STEP 3 Preparing the injection site[2]

- Aseptic technique
  - Swab area 3 times with a povidone iodine preparation (Betadine) and let dry.
- Local anesthetic options
  - Lidocaine
  - Vapocoolant spray

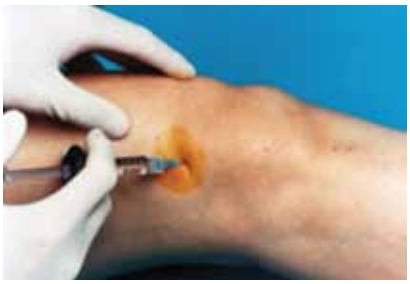


PHOTO COURTESY OF WEN DY. *AM FAM PHYSICIAN*. 2000[3]

STEP 4 Aspiration (skip to Step 5 if no effusion is present)

If effusion is present, aspiration of the effusion can relieve patient discomfort, be of diagnostic benefit, and avoid dilution of a viscosupplement to be injected.[2]

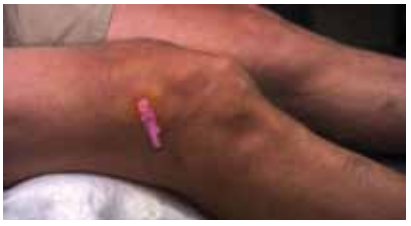
- Insert 1 1/2" 18-gauge needle for aspiration[3]
- If needle is accurately placed, the syringe should fill with fluid[1]
- Compression of the opposite side of the joint or the patella may aid in arthrocentesis.[3]

PHOTO COURTESY OF McNABB JW.
http://5minuteconsult.com/videos/McJSTI01KneeJointAspInj.html

STEP 5 Injection

If aspiration was required, the same needle can be used for aspiration and injection by changing the syringe.

- Insert needle (1 1/2", 21-gauge for corticosteroids; 1 1/2", 20- or 22-gauge for viscosupplementation) 3/4" to 1 1/4" for injection
- Remove needle, wipe off povidone iodine solution, and apply bandage.



PHOTOS COURTESY OF McNABB JW.
http://5minuteconsult.com/videos/McJSTI01KneeJointAspInj.html

Post-injection care: Setting patient expectations and managing adverse effects

- Patient should avoid strenuous activity for 1 to 2 days after injection and apply ice to injection site
- Mild pain or swelling at the injection site can occur, but is rare
  - If mild pain or swelling occurs, recommend ice, nonsteroidal anti-inflammatory drug (NSAID), rest, and elevation
  - If significant pain or swelling occurs:
- Joint aspiration
- Send aspirate to lab to rule out joint infection
- Crystal analysis
- May provide intra-articular corticosteroid to decrease pain and inflammation after viscosupplementation if infection has been excluded. ■

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1. Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. *J Bone Joint Surg Am*. 2002;84-A(9):1522-1527.
2. Waddell DD. The tolerability of viscosupplementation: low incidence and clinical management of local adverse events. *Curr Med Res Opin*. 2003;19(7):575-580.
3. Wen DY. Intra-articular hyaluronic acid injections for knee osteoarthritis. *Am Fam Physician*. 2000;62(3):565-570, 572.

Osteoarthritis as a Chronic Disease: Maximizing Management in Primary Care

POST-TEST

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