

Diagnosis and Treatment of Hip and Knee Osteoarthritis

A Review

Jeffrey N. Katz, MD, MSc; Kaetlyn R. Arant, BA; Richard F. Loeser, MD

IMPORTANCE Osteoarthritis (OA) is the most common joint disease, affecting an estimated more than 240 million people worldwide, including an estimated more than 32 million in the US. Osteoarthritis is the most frequent reason for activity limitation in adults. This Review focuses on hip and knee OA.

OBSERVATIONS Osteoarthritis can involve almost any joint but typically affects the hands, knees, hips, and feet. It is characterized by pathologic changes in cartilage, bone, synovium, ligament, muscle, and periarticular fat, leading to joint dysfunction, pain, stiffness, functional limitation, and loss of valued activities, such as walking for exercise and dancing. Risk factors include age (33% of individuals older than 75 years have symptomatic and radiographic knee OA), female sex, obesity, genetics, and major joint injury. Persons with OA have more comorbidities and are more sedentary than those without OA. The reduced physical activity leads to a 20% higher age-adjusted mortality. Several physical examination findings are useful diagnostically, including bony enlargement in knee OA and pain elicited with internal hip rotation in hip OA. Radiographic indicators include marginal osteophytes and joint space narrowing. The cornerstones of OA management include exercises, weight loss if appropriate, and education—complemented by topical or oral nonsteroidal anti-inflammatory drugs (NSAIDs) in those without contraindications. Intra-articular steroid injections provide short-term pain relief and duloxetine has demonstrated efficacy. Opiates should be avoided. Clinical trials have shown promising results for compounds that arrest structural progression (eg, cathepsin K inhibitors, Wnt inhibitors, anabolic growth factors) or reduce OA pain (eg, nerve growth factor inhibitors). Persons with advanced symptoms and structural damage are candidates for total joint replacement. Racial and ethnic disparities persist in the use and outcomes of joint replacement.

CONCLUSIONS AND RELEVANCE Hip and knee OA are highly prevalent and disabling. Education, exercise and weight loss are cornerstones of management, complemented by NSAIDs (for patients who are candidates), corticosteroid injections, and several adjunctive medications. For persons with advanced symptoms and structural damage, total joint replacement effectively relieves pain.

JAMA. 2021;325(6):568-578. doi:10.1001/jama.2020.22171

[+ Multimedia](#)

[← Related article page 581](#)

[+ CME Quiz at jamacmelookup.com and CME Questions page 583](#)

Author Affiliations: Orthopedic and Arthritis Center for Outcomes Research, Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Katz, Arant); Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Katz); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Katz); Thurston Arthritis Research Center, Division of Rheumatology, Allergy, and Immunology, University of North Carolina at Chapel Hill (Loeser).

Corresponding Author: Jeffrey N. Katz, MD, MSc, Orthopedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, 75 Francis St, Hale 5016, Boston, MA 02115 (jnkatz@bwh.harvard.edu).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Deputy Editor.

Long characterized as a wear-and-tear disorder, osteoarthritis (OA) is now understood to have a complex pathophysiology affecting multiple joints and joint structures, as captured by the Osteoarthritis Research Society International definition of OA: "The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."¹

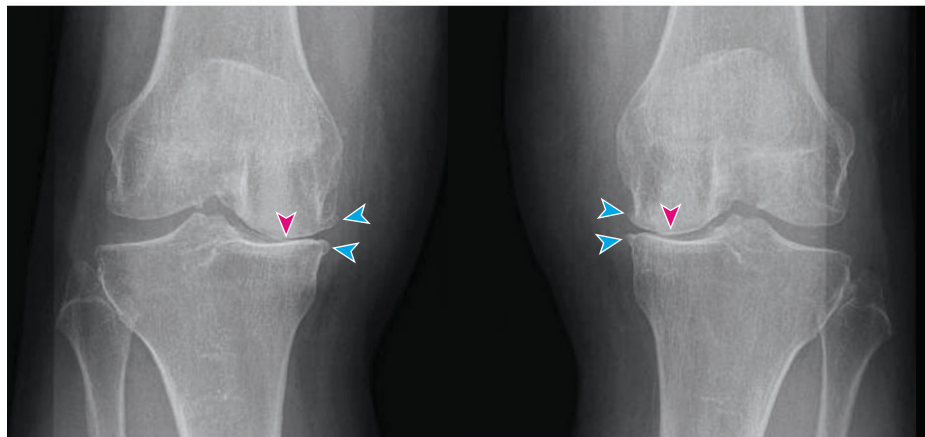
Worldwide, an estimated more than 240 million persons have symptomatic, activity-limiting OA, including an estimated more than 32 million in the US.^{2,3} The knee and hip are 2 commonly affected joints and are the focus of this Review. Nearly 30% of individuals older than 45 years have radiographic evidence of knee OA, about half of whom have knee symptoms.^{4,5} The prevalence of symptomatic, radiographic hip OA is around 10%.^{6,7}

The lifetime risk of symptomatic knee OA is greater in obese persons (body mass index ≥ 30) than in nonobese persons (19.7% vs 10.9%).⁸ Prior joint trauma, such as anterior cruciate ligament rupture and ankle fracture, increases risk, accounting for 12% of knee OA cases.⁹ The prevalence of symptomatic, radiographic knee OA was 11.4% in women and 6.8% in men in one large cohort study⁴ and 18.7% in women and 13.5% in men in another large cohort study.⁵ Compared with men with OA, women have more severe radiographic findings and symptoms.¹⁰ Older age and female sex are risk factors for hip OA as well as knee OA. In addition, congenital and acquired anatomic abnormalities (eg, hip dysplasia) are risk factors for hip OA. Regarding race, African American and White persons have similar prevalence of hip OA (accounting for race, sex, and body mass index), while African American individuals, especially women, have higher prevalence of knee OA.^{5,7}

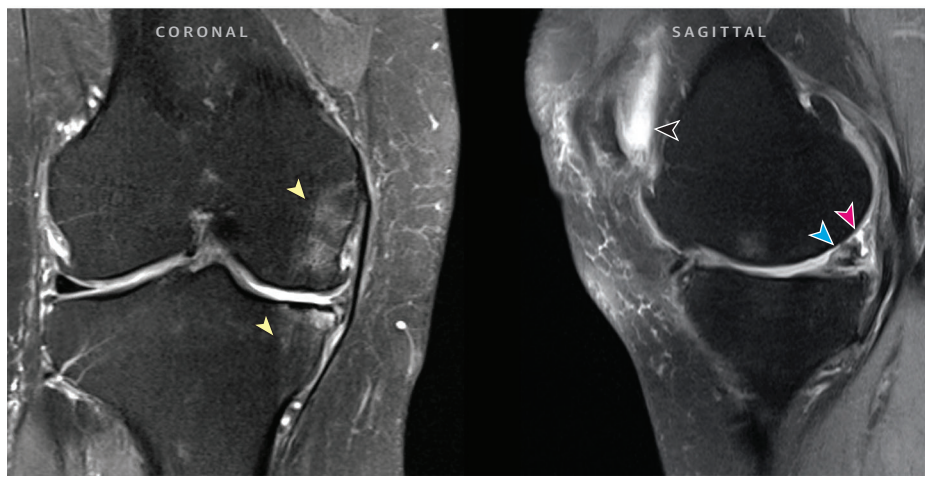
Osteoarthritis leads to substantial cost and mortality. Forty-three percent of the 54 million individuals in the US living with

Figure 1. Imaging of Knee Osteoarthritis

A Bilateral varus deformity with medial joint space narrowing and osteophyte formation



B MRI (proton density, fat saturated) of right knee of 63-year-old female patient



MRI indicates magnetic resonance imaging. A, Magenta arrowheads show joint space narrowing; cyan arrowheads, medial marginal osteophytes. B, On coronal view, yellow arrowheads are bone marrow lesions; on sagittal view, magenta arrowhead is meniscal damage, cyan arrowhead is cartilage damage, and black arrowhead is retropatellar effusion.

arthritis (most of whom have OA) experience arthritis-related limitations in daily activities.¹¹ Wage losses due to OA amount to \$65 billion and direct medical costs exceed \$100 billion.^{2,12} Persons with knee OA spend an average of about \$15 000 (discounted) over their lifetimes on the direct medical costs of OA.¹³ Osteoarthritis is commonly associated with comorbidities, which may stem from lack of physical activity, medication toxicity, and the effects of inflammatory cytokines. It has been estimated that 31% of persons with OA have at least 5 comorbid conditions.² Persons with hip and knee OA have approximately 20% excess mortality compared with age-matched controls, in part because of lower levels of physical activity.²

Methods

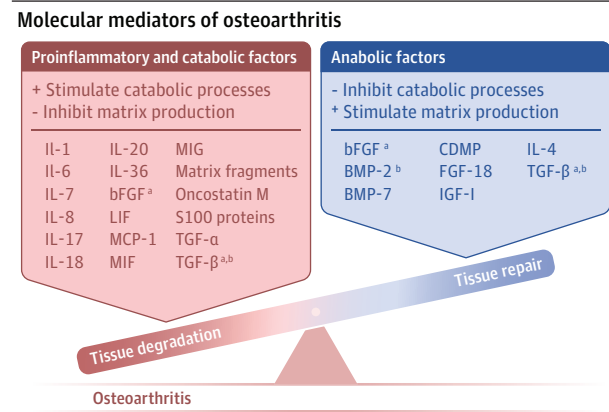
We searched PubMed from January 1957 to June 2020 for English-language articles on the diagnosis and management of hip and knee OA using the search terms *osteoarthritis* and *treatment*; *osteoarthritis* and *epidemiology*; *osteoarthritis* and *diagnosis or imaging*; and *osteoarthritis* and *disability or comorbidity*. We reviewed these pub-

lications and the relevant references in these articles. We based our conclusions on treatment efficacy primarily using the rigorous systematic literature syntheses and meta-analyses that support the Osteoarthritis Research Society International 2018 OA treatment guidelines.¹⁴ The efficacy parameter in these studies is the standardized mean difference (SMD), the mean difference in improvement between active treatment and placebo divided by the standard deviation of the difference. For questions not addressed by the meta-analyses, we provide results of pivotal trials.

Pathophysiology

Osteoarthritis arises from complex biological processes that include cartilage, bone, synovium, ligaments, periarticular fat, meniscus, and muscle.¹⁵ The classic features of OA noted on radiographs include joint space narrowing due to loss of articular cartilage and meniscus and bony changes including sclerosis of subchondral bone and osteophytes (Figure 1A). The effects of OA on cartilage, meniscus, synovium, subchondral bone, and other structures can be seen on magnetic resonance imaging (MRI) (Figure 1B).

Figure 2. Molecular Mediators of Osteoarthritis



bFGF indicates basic fibroblast growth factor; BMP, bone morphogenetic protein; CDMP, cartilage-derived morphogenetic protein; FGF-18, fibroblast growth factor 18; IGF, insulinlike growth factor; IL, interleukin; LIF, leukemia inhibitory factor; MCP-1, monocyte chemoattractant protein 1; MIF, macrophage migration inhibitory factor; MIG, monokine induced by interferon γ ; TGF, transforming growth factor. A number of proinflammatory factors and anabolic factors are present in joint tissues and in the synovial fluid. Proinflammatory mediators contribute to joint tissue destruction in large part by stimulating production of matrix degrading enzymes, including the matrix metalloproteinases, but also through inhibition of matrix synthesis. The anabolic factors stimulate matrix production and, in some cases, also inhibit the catabolic signaling stimulated by proinflammatory mediators. Some factors including TGF- β and bFGF are capable of initiating either catabolic or anabolic activity depending on cell type and specific receptors expressed. TGF- β and BMP-2 can also stimulate osteophyte formation. The overall activity in the osteoarthritic joint is tipped in favor of the proinflammatory side.

^a Stimulate anabolic or catabolic processes depending on cell type and receptor expression.

^b Can stimulate osteophyte formation.

The biomechanical environment influences the disease process. Varus alignment of the lower extremities ("bowleg") shifts load medially, increasing risk of medial compartment knee OA, while valgus alignment ("knocked knees") shifts load laterally, leading to lateral compartment OA. These abnormalities in alignment are risk factors for OA incidence and, more importantly, for OA progression.^{16,17} Excessive loading of bone may result in bone marrow lesions, seen on MRI (Figure 1B).¹⁸ Histologically, bone marrow lesions contain microfractures with bone fragments, necrosis, fibrosis, and abnormal adipocytes suggestive of focal areas of damage and remodeling due to abnormal loading.¹⁹

Synovitis is commonly noted in OA joints.²⁰ The synovitis seen in OA has a predominance of macrophages, while the synovitis of rheumatoid arthritis has a predominance of T cells.²¹ This reflects activation of the innate immune response in OA joints, likely due to damage of joint tissues resulting in a chronic wound type of environment.²² Osteoarthritis synovitis is more focal than in rheumatoid arthritis; in the knee, it is commonly found in the suprapatellar pouch.²³ Synovitis plays a prominent role in joint destruction in rheumatoid arthritis, while its role in the progression of OA may be limited to a subset of individuals.

Many proinflammatory cytokines and growth factors have been identified in the OA joint (Figure 2). Cytokines present at relatively high levels in OA synovial fluid include interleukin (IL) 6, monocyte chemoattractant protein 1, vascular endothelial growth

factor, interferon γ -induced protein, and monokine induced by interferon γ .²⁴ The proinflammatory factors are responsible for the progressive destruction and remodeling of the joint through the stimulation of matrix-degrading enzymes, including the matrix metalloproteinases.^{15,25} The growth factors that normally would stimulate matrix production and repair of joint tissues are overwhelmed by proinflammatory mediators. Certain growth factors including transforming growth factor β and bone morphogenetic protein 2 promote osteophyte formation and contribute to subchondral sclerosis. The proinflammatory mediators and anabolic factors are produced locally by the cells within the affected tissues, including the articular chondrocytes, synovial fibroblasts, and immune cells in the synovium; inflammatory cells in periarticular fat; and cells in bone, including osteoblasts, osteocytes, osteoclasts, and bone marrow mesenchymal stem cells (Figure 3).^{15,26} The cytokines are potential targets for disease modification in OA; however, currently it is not clear which cytokines are primary drivers of joint destruction and which are involved secondarily.

Clinical Presentation

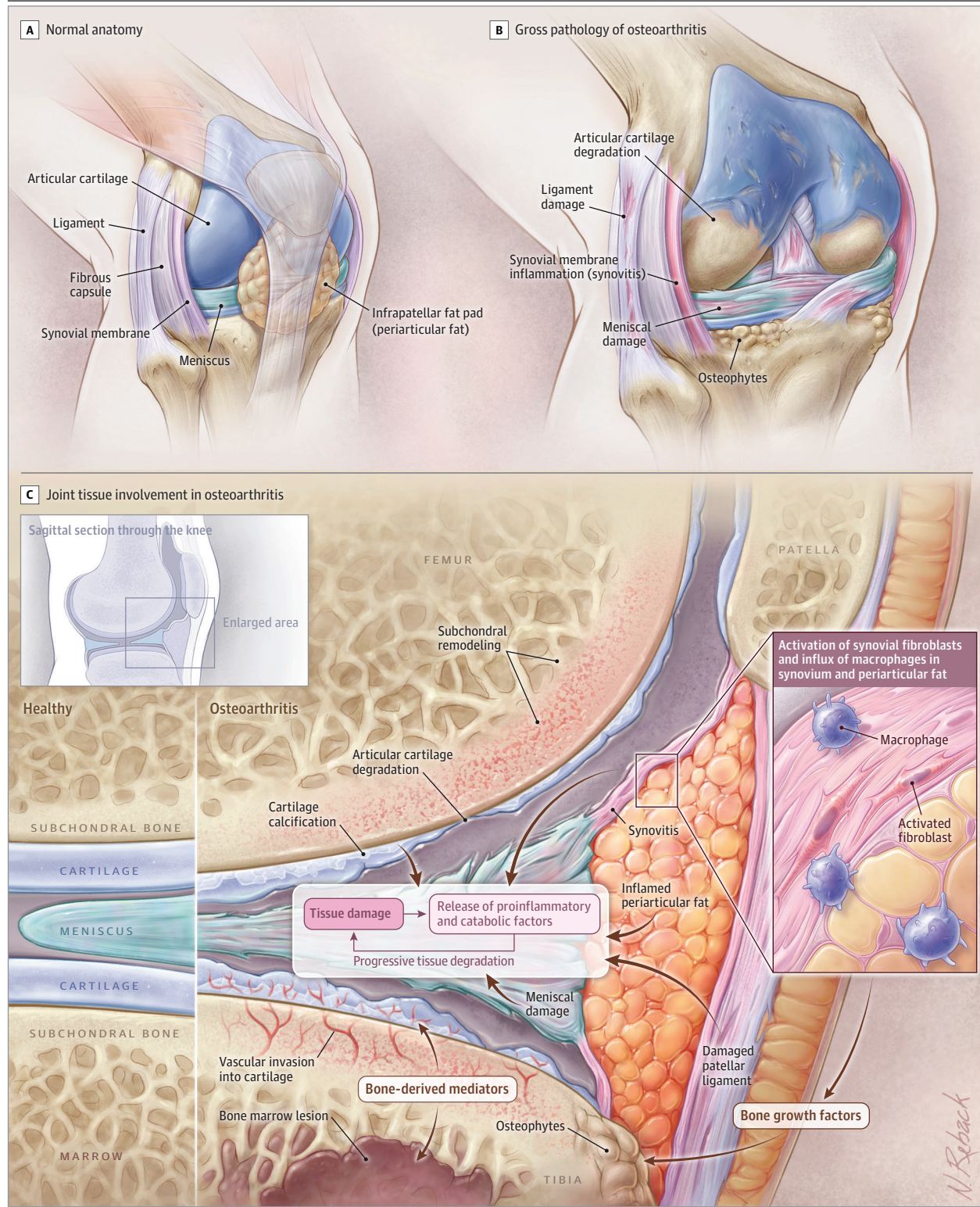
Patients with OA typically present with pain and stiffness in the affected joint(s). Stiffness is worse in the morning or on arising after prolonged sitting and improves within 30 minutes. Pain is use related early in the course but can become less predictable over time. Although OA is sometimes viewed as a disease of inexorable worsening, natural history studies show that most patients report little change in symptoms over 6 years of observation.²⁷

Assessment and Diagnosis

Clinicians must distinguish symptomatic OA from other entities that can cause hip or knee pain, including inflammatory (eg, rheumatoid and psoriatic) arthritis, infectious and crystalline (eg, gout, pseudogout) arthritis, and soft tissue lesions such as bursitis, tendinitis, and meniscal tear. The stiffness in inflammatory arthritis may last more than an hour. The pain of infectious arthritis and crystalline arthritis is typically acute. Individuals with retropatellar pain may have patellofemoral OA, which can exist in isolation or in the presence of tibiofemoral OA. Because the patellofemoral joint is loaded when the knee is bent, patellofemoral OA is especially painful when patients ascend and descend stairs and get into and out of cars or a bath.²⁸ The syndrome of patellofemoral pain is common and often arises from malalignment of the patella in the femoral groove (eg, due to asymmetric tension from the lateral and medial quadriceps) rather than from OA.

On physical examination, knee effusions are generally either absent or small and at body temperature in persons with OA. Those with effusions may have popliteal or Baker cysts, which are extensions of the synovial swelling that can be palpated in the posterior aspect of the knee. In contrast, the knee often has warm, easily palpable effusions in inflammatory, infectious, and crystalline arthritis. Soft tissue lesions such as anserine bursitis and trochanteric bursitis are extra-articular and do not cause joint effusions; they are identified by local tenderness. Effusions cannot be detected on physical examination of recessed joints such as the hip. Infectious,

Figure 3. Joint Tissue Involvement in Osteoarthritis



Osteoarthritis can involve all joint structures at some point in the disease process. Although articular cartilage degradation and loss is a central feature, changes in the neighboring bone accompany the cartilage damage. These include subchondral bone remodeling, resulting in increased thickness, osteophytes, bone marrow lesions, and vascular invasion into the overlying

cartilage. Inflammatory cells, primarily macrophages, are present in the synovium and can also be noted in periarticular fat. Meniscal and ligament damage is often found as well. All of these tissues are capable of producing a host of proinflammatory factors and matrix-degrading enzymes and thus contribute to the progressive remodeling and destruction of the joint.

Commonly Asked Questions About Osteoarthritis (OA)

How Common Is OA?

Osteoarthritis is among the most frequently seen problems in adult clinical practice. It affects an estimated more than 240 million persons worldwide and an estimated more than 32 million persons in the US.

Who Is Mostly Likely to Get OA?

The risk of OA increases markedly with age. Osteoarthritis is exceedingly rare in persons younger than 30 years, while one-third of individuals older than 75 years have symptomatic knee OA. Osteoarthritis is more common in women than in men. Other important risk factors of OA include obesity, prior joint injury, genetics, and malalignment of joints.

How Is OA Diagnosed?

The cardinal symptom of OA is pain, which is typically provoked by load bearing and relieved by rest. Stiffness occurs following inactivity. On physical examination, bony overgrowth can often be appreciated and pain can often be provoked by joint motion. Radiographs typically reveal osteophyte formation and narrowing of the joint space, the latter reflecting loss of cartilage.

Is OA a Wear-and-Tear Disease?

Osteoarthritis was long considered a wear-and-tear disease of articular cartilage caused by prolonged use of joints, but understanding of the disorder has advanced considerably. Pathologic changes in OA involve cartilage, bone, synovium, ligament, adipose tissue, and meniscus, as well as neurologic pathways involving pain processing. These changes can arise from external mechanical loads (including obesity), joint malalignment, joint injury, and metabolic and genetic factors. Pathologic features include inflammation. These insights have prompted an array of therapies that may soon permit clinicians to arrest the progression of joint damage and attendant symptoms.

What Treatments Are Used for OA?

Management of OA begins with educating patients about its natural history, the benefits of exercise and weight loss, and strategies to reduce pain. Weight loss and physical therapy have well-documented benefits in persons with knee OA. Nonsteroidal anti-inflammatory drugs, given either topically or orally, are the backbone of pharmacologic treatment. Duloxetine has proven efficacy. Intra-articular injections of corticosteroids provide temporary relief. Injection of hyaluronic acid products is also offered frequently, although evidence of benefit remains disputed. Injections of biologic therapies (such as platelet-rich plasma or stem cells) have not been studied rigorously. Joint replacement is highly effective for advanced OA of the knee and hip.

How Effective Is Total Joint Replacement? What Are the Risks?

How Long Does the Implant Last?

About 90% of recipients of total hip replacement and about 80% of recipients of total knee replacement report substantial improvement in pain. Mortality following these procedures is less than 1%, and serious problems such as pulmonary embolus, myocardial infarction, pneumonia, and infection of the implant occur in less than 5%. The implants are durable, with about 90% of knee implants and 80% of hip implants lasting 20 years. These procedures appear to be underused in African American and Hispanic persons with advanced OA.

crystalline, and other inflammatory arthritides can be distinguished incisively from OA because the synovial fluid white blood cells exceed 2/ μ L in these disorders.

The sensitivities, specificities, and likelihood ratios of various elements of the physical examination and radiographic features for hip and knee OA are shown in Table 1. When present, bony enlargement on physical examination is very specific (95%) for establishing a diagnosis of knee OA, though somewhat insensitive (55%), while crepitus is sensitive (89%), though somewhat nonspecific (58%).³¹ Osteophytes on knee radiographs are both sensitive (91%) and fairly specific (83%). The combination of osteophytes and knee pain has good sensitivity (83%) and specificity (93%), with a likelihood ratio of 11.9.³¹ (Likelihood ratio = sensitivity/[1 – specificity]). If the likelihood ratio is greater than 1, a positive test result indicates that the posttest probability of disease is greater than the pretest probability.)

A recent review provided detailed data on the utility of physical examination maneuvers in the diagnosis of hip OA and a video demonstration of the hip examination.²⁹ Hip internal rotation of less than 15° is moderately sensitive (66%) and specific (72%), as is limited hip adduction (80% sensitive, 81% specific).^{29,30} Pain with hip internal rotation is more sensitive (82%) but less specific (39%). Osteophytes on radiographs are both sensitive (89%) and specific (90%). The combination of hip pain plus an osteophyte is also quite sensitive (89%) and specific (90%).³⁰

These data suggest that a presumptive diagnosis of hip or knee OA can be made on the basis of history and physical examination. Radiographs portray the severity of structural damage and improve specificity when osteophytes or joint space narrowing are present. Pathologic features and symptoms of OA can occur before osteophytes are present on radiographs. Thus, normal radiographic findings do not exclude OA. If the clinical presentation is highly suggestive of OA, clinicians should initiate management (detailed below) despite normal radiographs. Knee radiographs should be performed with the patient standing to reveal the extent of joint space narrowing of the tibiofemoral joint. For research purposes, hip and knee radiographs are typically assessed with the Kellgren-Lawrence grading system, with grade 0 representing no pathologic findings; grade 1, questionable osteophytes; grade 2, definite osteophytes; grade 3, definite joint space narrowing; and grade 4, advanced joint space narrowing.^{32,33} The radiograph in Figure 1A is Kellgren-Lawrence grade 3 and nearly grade 4 because the advanced medial joint space narrowing is nearly bone on bone.

Hip radiographs typically include an anteroposterior view and a lateral view. Weight bearing is not necessary. The interrater and intrarater reliabilities of hip radiographs for detecting joint space narrowing are high.³⁴ Hip radiographs involve greater exposure to ionizing radiation than radiographs of the chest or knee.

Magnetic resonance imaging is seldom indicated in the assessment or management of knee or hip OA. Magnetic resonance imaging detects changes in cartilage, meniscus (knee), labrum (hip), bone, and synovium, providing a fuller picture of pathological involvement (Figure 1B).³⁵ Because of its high sensitivity,³⁵ MRI is useful for research studies to identify early OA and document structural changes over time. In clinical care, MRI can be useful if there is suspicion of conditions such as subchondral insufficiency fracture, tumor, or infection that would be treated differently and more urgently than OA.

Ultrasound can visualize joint effusion, osteophytes, and other features.³⁶ Compared with MRI, ultrasound has sensitivity and specificity exceeding 85% for detecting osteophytes. Ultrasound is not as accurate as MRI in assessing joint space narrowing.³⁷ Because ultrasound is less expensive and more portable than MRI, it is used

Table 1. Performance Characteristics of Key Physical Examination and Radiographic Features of Hip and Knee Osteoarthritis^{29,30}

Features	Sensitivity, %	Specificity, %	Likelihood ratio
Knee			
Bony enlargement	55	95	11.0
Crepitus with passive motion	89	58	2.1
Osteophytes	91	83	5.4
Knee pain plus osteophytes	83	93	11.9
Hip			
Internal rotation <15°	66	72	2.4
Pain with internal rotation	82	39	1.3
Decreased hip adduction	80	81	4.2
Femoral or acetabular osteophytes	89	90	8.9
Superior joint space narrowing	85	66	2.5
Hip pain plus osteophytes	89	90	8.9

Table 2. Approach to Management of Patients With Osteoarthritis

Type of therapy	Specific therapy	Comments
Nonpharmacologic therapies	Exercise, education, weight loss (if obese), yoga/tai chi	<ul style="list-style-type: none"> Physical therapist can provide structured exercise, especially if patient lacks confidence or knowledge. Weight loss is effective but difficult to achieve and sustain. Yoga and tai chi are beneficial, with few risks.
Anti-inflammatory agents	Topical NSAIDs, oral NSAIDs, COX-2 inhibitors	<ul style="list-style-type: none"> Topical NSAIDs are generally less toxic than oral NSAIDs. Use COX-2 inhibitors if patient is taking anticoagulant or in case of gastrointestinal toxicity.
Intra-articular injections	Corticosteroids, hyaluronic acid compounds	<ul style="list-style-type: none"> Injections are most useful in monoarticular presentations. Steroid injections have a risk of hyperglycemia and infection; benefits last a few weeks to months. Long-acting steroid compound may offer advantages. Hyaluronic acid compounds are more costly, with conflicting evidence of efficacy. Stem cells, platelet-rich plasma, and other growth factors are not recommended because of lack of efficacy data.
Additional medications	Duloxetine, opioids	<ul style="list-style-type: none"> Duloxetine is efficacious, though may be difficult to tolerate. Opioid adverse effects are numerous and serious; reserve for short-term use or when there are no other options; tramadol is preferred over stronger opioids.
Surgery	Arthroscopy, total joint replacement	<ul style="list-style-type: none"> Arthroscopy is not indicated for osteoarthritis per se but is reasonable in osteoarthritis and meniscal tear in cases of no response to physical therapy. Joint replacement is effective and cost-effective; it is underused in Black and Hispanic persons.

Abbreviations: COX-2, cyclooxygenase 2; NSAID, nonsteroidal anti-inflammatory drug.

frequently in Europe and in a growing number of US centers in diagnosis of OA and assessment of progression.

Treatment

The approach to management of patients with OA is outlined in Table 2. Several professional organizations have developed guidelines for OA management (Figure 4). The guidelines suggest that patients with OA should be offered a core set of nonpharmacological interventions including education, weight loss (for those who are overweight), and exercises (strengthening, cardiovascular, and/or mind-body exercises such as yoga or tai chi).^{14,38-43}

Structured exercise interventions that typically focus on strengthening of lower extremity muscles offer improvements in pain and functional status (SMD of 0.52 for knee OA and 0.34 for hip OA) (Table 3). A randomized clinical trial of a structured walking program showed a reduction in pain scores of 1.4 points (on a 0- to 10-point scale) in the walking group and just 0.1 point in the control group ($P = .003$).⁴⁴ Referral to a physical therapist is appropriate to initiate such a program or to address lower extremity weakness or limitations in hip or knee range of motion. A combination of diet and exercise can result in substantial weight loss, pain relief, improvement

in functional status, and reduction in inflammatory markers compared with exercise alone.⁴⁵

Although trials of lateral wedge shoe inserts have not shown efficaciousness, a recent trial of an individualized external orthotic (attached below the sole) was associated with greater improvement in pain and functional status than a control orthotic.⁴⁶ This observation should be replicated before being advanced to routine use.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line pharmacologic treatment for OA. In numerous placebo-controlled trials, NSAIDs have resulted in greater pain relief than placebo, with SMDs in pain and function scores of approximately 0.33 SD, reflecting a moderate effect (Table 3). Many NSAIDs are available over the counter. Topical NSAIDs generally have less gastrointestinal toxicity than oral NSAIDs^{14,40} but are less useful in hip OA because the joint is recessed.

Nonsteroidal anti-inflammatory drugs have important toxicities, including gastrointestinal irritation and ulceration, bleeding, and decreased renal blood flow with azotemia. Patients taking anticoagulants who wish to take an NSAID should use a cyclooxygenase 2 inhibitor (such as celecoxib), which does not increase bleeding. Patients with dyspepsia should use proton pump inhibitors and/or a cyclooxygenase 2 inhibitor. Patients with history of bleeding peptic ulcer are typically not prescribed NSAIDs at all. Risk factors for gastrointestinal bleeding due to NSAIDs include older age, medical

Figure 4. Summary of Osteoarthritis Treatment Guidelines From Major Professional Societies^{14,38-40}

Recommendations	ACR		EULAR		AAOS		OARSI	
	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip
Nonpharmacologic treatments								
Weight loss (overweight or obese individuals)	●	●	●	●	●		●	●
Self-management/education programs (eg, goal setting, skill building, education about exercise and medication)	●	●	●	●	●		●	●
Physical exercise (eg, combination of aerobic exercise, strengthening, neuromuscular training, isometric exercises)	●	●	●	●	●		●	●
Balance training	●	●					●	●
Yoga	●						●	●
Tai chi	●	●					●	●
Cognitive behavior therapy	●	●						●
Acupuncture	●	●			●		●	●
Transcutaneous electrical nerve stimulation	●	●			○			
Pharmacologic treatments								
Oral NSAIDs	●	●		●	●	●	●	●
Topical NSAIDs	●				●	●	●	
Acetaminophen (short-term relief only)	●	●			○		●	●
Tramadol	●	●			●			
Nontramadol opioids	●	●					●	●
Duloxetine	●	●					●	●
Glucosamine or chondroitin	●	●			●	●	●	
Hyaluronic acid injection	●	●			●	●	●	●
Glucocorticoid steroid injection	●	●			○	●	●	●
Growth factor injections and/or platelet-rich plasma	●	●			○			

● Strongly recommended ● Conditionally recommended against ○ Inconclusive
 ● Conditionally recommended ● Strongly recommended against

AAOS indicates American Academy of Orthopaedic Surgeons; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NSAID, nonsteroidal anti-inflammatory drug; OARSI, Osteoarthritis Research Society International. EULAR does not distinguish between strong and conditional recommendations. In this figure, any recommendation with a level of evidence of 1 (out of 4) and a level of agreement of 8.5 (out of 10) or above is considered strongly recommended. The AAOS includes 3 levels of evidence: strong, moderate, and limited. In this figure, any recommendation that has moderate or limited evidence is considered conditionally recommended.

comorbidities, and concomitant use of corticosteroids and anticoagulants.⁴⁷ Individuals with cardiovascular or renal disease are at risk of renal toxicity; alternatives to NSAIDs should be discussed. Acetaminophen is less efficacious than NSAIDs in management of knee (SMD, 0.05) and hip (SMD, 0.23) OA.⁴⁸⁻⁵² It is a reasonable, safe alternative for those intolerant to NSAIDs but should not be used in persons with liver disease or risk factors such as heavy alcohol use. The Table published in the Medical Letter in this issue of *JAMA* provides rich information on formulations, dosages, and costs of many of the pharmacologic agents noted in this Review.

Patients unable to take NSAIDs or who do not respond to NSAIDs can be given intra-articular corticosteroid injections, which typically re-

lieve pain for a few weeks.⁵³ They are especially helpful in patients with OA of a single joint that can be injected easily, such as the knee. The hip is generally injected under imaging (fluoroscopy or ultrasound) guidance. Corticosteroid injections have no greater effect on pain than placebo after 3 months⁵⁴ and may be inferior to physical therapy at 1 year.⁵⁵ A newer formulation of steroid injection (extended-release triamcinolone acetonide) appears to have fewer systemic effects than traditional steroid injections.⁵⁶ Some studies have suggested that intra-articular steroid injections may have deleterious effects on cartilage^{54,57}; the clinical meaning of these findings is not yet known.

Injection of intra-articular hyaluronic acid products is another option for patients with persistent pain despite NSAID use. Guidelines

differ regarding recommendations of intra-articular hyaluronic acid (Figure 4).^{14,39-43} Although efficacy of hyaluronic acid injections is similar to that of NSAIDs (SMD, 0.37) (Table 3), the highest-quality trials showed weaker effects. Injection of growth factors, such as those found in platelet-rich plasma, and injection of stem cell preparations are increasing in use. However, these products are nonstandardized and studies of these agents are weak.

Osteoarthritis pain may be mediated in part by mechanisms in the central nervous system. Several medications have been used to address pain of central origin. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been shown in randomized trials to result in greater pain relief than placebo in persons with knee OA (SMD, 0.39).^{58,59} Gabapentin may have efficacy in knee OA, but evidence is limited.⁶⁰ Opiate analgesics are used by more than 20% of patients with OA but have limited efficacy for hip and knee OA (SMD, ≈0.20) and considerable toxicity, including constipation, falls, somnolence, respiratory depression, and potential for addiction. Osteoarthritis treatment guidelines advise against use of stronger opiates, with conditional recommendation of tramadol, a synthetic opioid agonist that also inhibits reuptake of serotonin and norepinephrine.⁴⁰

To date, trials of biologics to inhibit IL-1 or tumor necrosis factor α in knee OA have failed to find that these biologics relieve symptoms or halt structural progression compared with placebo.⁶¹⁻⁶³ However, a secondary analysis of the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) demonstrated a significant reduction in the incidence of hip and knee replacement in those receiving anti-IL-1 β , with a pooled hazard ratio of 0.58 (95% CI, 0.42-0.80; $P = .001$).⁶⁴ Some areas of current investigation for disease modification that are being examined in early-phase studies include Wnt inhibition⁶⁵; intra-articular injection of an anabolic growth factor, fibroblast growth factor 18⁶⁶; and a cathepsin K inhibitor.⁶⁷

Patients with persistent pain and functional loss and advanced radiographic changes are candidates for total knee replacement (TKR) or total hip replacement (THR). More than 700 000 primary TKRs and 330 000 primary THRs are performed annually in the US, more than 90% of which are for OA.⁶⁸ Ninety-day mortality is less than 1%, and serious complications at 90 days occur in less than 5%.⁶⁹⁻⁷² About 90% of recipients of THR and 80% of recipients of TKR report little to no residual pain following recovery from these procedures.⁷³ A randomized clinical trial of TKR vs a rigorous physical therapy program showed that those receiving TKR improved on the Knee Injury and Osteoarthritis Outcome Score by 35 points (on a 0- to 100-point scale) compared with 17 points in those receiving physical therapy (difference, 17 points; 95% CI, 10.4-23.8).⁷⁴ Less than 10% of TKRs and approximately 20% of THRs need to be revised over 20 years.^{75,76} The failure rate is higher in younger and more active recipients, those with comorbidities, and those operated on in low-volume centers or by low-volume surgeons.^{77,78} The generally low revision rates mean that persons who receive TKR or THR after age 70 years are much more likely to die with their original implants in place than to need revision.⁷⁹ In patients with unicompartmental knee OA, surgical options include unicompartmental knee replacement and osteotomy as well as TKR. Arthroscopic debridement is not appropriate for treating OA; arthroscopic partial meniscectomy has a limited role in patients with OA and symptomatic meniscal tear for whom nonoperative therapy was not helpful.⁸⁰⁻⁸²

Black and Hispanic individuals are about 25% less likely to receive TKR than non-Hispanic White individuals, even after account-

Table 3. Standardized Mean Differences in Pain Score From Placebo-Controlled Trials of 4 to 12 Weeks' Duration¹⁴

	Standardized mean difference (95% CI)	
	Knee osteoarthritis	Hip osteoarthritis
Structured exercise program	0.52 (0.37 to 0.68)	0.34 (0.19 to 0.49)
Mind-body programs ^a	0.63 (0.32 to 0.95)	0.35 (-0.06 to 0.76)
Dietary weight management ^b	0.42 (0.23 to 0.62)	No trials
Acetaminophen	0.05 (-0.11 to 0.21)	0.23 (0.13 to 0.33)
Nonsteroidal anti-inflammatory drugs		
Oral	0.28 (0.22 to 0.35)	0.33 (0.24 to 0.43)
Topical	0.20 (0.11 to 0.29)	No trials
Duloxetine	0.39 (0.25 to 0.52)	No trials
Opioids	0.20 (0.05 to 0.35)	0.21 (0.10 to 0.32)
Intra-articular injections		
Corticosteroids	0.41 (0.21 to 0.61)	1.65 (0.16 to 3.47)
Hyaluronic acid	0.34 (0.26 to 0.42)	0.18 (-0.13 to 0.50)

^a Includes tai chi and yoga.

^b Dietary weight management plus exercise vs exercise alone.

ing for age and socioeconomic status.^{71,83} These patterns are seen for THR as well.^{84,85} Proposed reasons for these disparities include less frequent offers of joint replacement to non-White individuals,⁸⁶ less willingness to undergo total joint replacement, implicit bias, and other factors.^{87,88} Black and Hispanic individuals also have a higher risk of adverse outcomes, including mortality after THR and joint infections following TKR.⁸⁹

Several innovative interventions for OA have been introduced into clinical use but have not been evaluated with sufficient rigor to be recommended. These include geniculate artery embolization, water-cooled radiofrequency ablation, and botulinum toxin injections.

Evolving Concepts in Management of OA

Osteoarthritis consists of multiple phenotypes.⁹⁰ Knee OA that develops after anterior cruciate ligament tear might have a mechanism distinct from OA that is associated with obesity. Individuals may have more than 1 mechanism at play, requiring multimodal management. It is important to determine which individuals with early OA are more likely to progress rapidly and would benefit from an intervention designed to slow disease progression. Machine learning approaches using data sets that include demographic, imaging, and biomarker data are being harnessed to identify such subsets.⁹¹

Intensive research has identified potential targets for structure-modifying therapies,⁶⁵⁻⁶⁷ including inhibitors of collagenases and aggrecanases that degrade cartilage and of the cytokines and chemokines that contribute to the proinflammatory environment.⁹² Preclinical evidence suggests that senescent cells in the joint contribute to OA by releasing proinflammatory mediators and matrix-degrading enzymes. Targeting these cells with senolytics that selectively kill senescent cells could be of value.⁹³ It remains unclear whether arresting progression of structural damage in OA ultimately results in reduced pain and functional limitation.

In addition to structure modification, research in OA therapeutics has also focused on nerve growth factor (NGF), with several trials showing efficacy in pain relief with injections of anti-NGF antibodies.⁹⁴⁻⁹⁶ However, individuals who received anti-NGF therapy were more likely than those receiving placebo to experience rapid progression of OA requiring joint arthroplasty, especially if they were also taking NSAIDs.⁹⁷ If anti-NGF therapy is approved for OA, clinicians and patients will need to discuss risks and benefits carefully.

Prognosis

Although some patients with OA follow a trajectory of steady increase in symptoms, others have waxing and waning pain over many years. There is also variability in the progression of joint damage. Model projections suggest that more than 50% of persons in the US with symptomatic knee OA undergo TKR during their lifetimes.¹³ Several factors influence the rapidity of radiographic and clinical progression including older age, reduced physical activ-

ity, extent of cartilage damage, short-term changes of cartilage damage, malalignment, and more severe pain.^{27,98,99}

Limitations

This Review is limited by the fact that the duration of most treatment studies is less than 1 year, whereas many patients have OA for decades. As a result, randomized trials shed little light on long-term outcomes.

Conclusion

Hip and knee OA are highly prevalent and disabling. Education, exercise and weight loss are cornerstones of management, complemented by NSAIDs (for patients who are candidates), corticosteroid injections, and several adjunctive medications. For persons with advanced symptoms and structural damage, total joint replacement effectively relieves pain.

ARTICLE INFORMATION

Accepted for Publication: October 23, 2020.

Author Contributions: Dr Katz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Katz, Loeser.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: Arant, Loeser.

Conflict of Interest Disclosures: Dr Katz reported receipt of research funding for a cohort study of patients with OA from Samumed and for a qualitative study of patients with OA from Flexion Therapeutics. Dr Loeser reported receipt of research funding for a preclinical study in OA from Bioventus and consulting fees from Unity Biotechnology. No other disclosures were reported.

Funding/Support: This work was supported by National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases grants P30AR072577 and P30 AR072520.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at [Edward.livingston@jamanetwork.org](mailto:livingston@jamanetwork.org) or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Kraus VB, Blanco FJ, Englund M, et al. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis Cartilage*. 2015;23(8):1233-1241. doi:10.1016/j.joca.2015.03.036

2. Hawker G. *Osteoarthritis as a Serious Disease*. Osteoarthritis Research Society International; 2016. Accessed January 12, 2021. <https://oarsi.org/research/oa-serious-disease>

3. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743-800. doi:10.1016/S0140-6736(15)60692-4

4. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. *Arthritis Rheum*. 1987;30(8):914-918. doi:10.1002/art.1780300811

5. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol*. 2007;34(1):172-180.

6. Haugen IK, Englund M, Aliabadi P, et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. *Ann Rheum Dis*. 2011;70(9):1581-1586. doi:10.1136/ard.2011.150078

7. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol*. 2009;36(4):809-815. doi:10.3899/jrheum.080677

8. Losina E, Weinstein AM, Reichmann WM, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care Res (Hoboken)*. 2013;65(5):703-711. doi:10.1002/acr.21898

9. Brown TD, Johnston RC, Saltzman CL, et al. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. *J Orthop Trauma*. 2006;20(10):739-744. doi:10.1097/O1.bot.0000246468.80635.ef

10. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. 2005;13(9):769-781. doi:10.1016/j.joca.2005.04.014

11. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2013-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(9):246-253. doi:10.15585/mmwr.mm6609e1

12. US Bureau of Labor Statistics. Consumer price index for all urban consumers (CPI-U): U.S. city average, by expenditure category. Accessed April 1, 2020. <https://www.bls.gov/news.release/cpi.t01.htm>

13. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. *Arthritis Care Res (Hoboken)*. 2015;67(2):203-215. doi:10.1002/acr.22412

14. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578-1589. doi:10.1016/j.joca.2019.06.011

15. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum*. 2012;64(6):1697-1707. doi:10.1002/art.34453

16. Brouwer GM, van Tol AW, Bergink AP, et al. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. *Arthritis Rheum*. 2007;56(4):1204-1211. doi:10.1002/art.22515

17. Sharma L, Song J, Felson DT, et al. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA*. 2001;286(2):188-195. doi:10.1001/jama.286.2.188

18. Felson DT, McLaughlin S, Goggins J, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med*. 2003;139(5 pt

- 1):330-336. doi:10.7326/0003-4819-139-5_Part-1-200309020-00008
19. Taljanovic MS, Graham AR, Benjamin JB, et al. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. *Skeletal Radiol*. 2008;37(5):423-431. doi:10.1007/s00256-008-0446-3
20. Felson DT, Niu J, Neogi T, et al. Synovitis and the risk of knee osteoarthritis: the MOST Study. *Osteoarthritis Cartilage*. 2016;24(3):458-464. doi:10.1016/j.joca.2015.09.013
21. Wood MJ, Leckenby A, Reynolds G, et al. Macrophage proliferation distinguishes 2 subgroups of knee osteoarthritis patients. *JCI Insight*. 2019;4(2):e125325. doi:10.1172/jci.insight.125325
22. Orlovsky EW, Kraus VB. The role of innate immunity in osteoarthritis: when our first line of defense goes on the offensive. *J Rheumatol*. 2015;42(3):363-371. doi:10.3899/jrheum.140382
23. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. *Bone*. 2012;51(2):249-257. doi:10.1016/j.bone.2012.02.012
24. Sohn DH, Sokolove J, Sharpe O, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. *Arthritis Res Ther*. 2012;14(1):R7-R7. doi:10.1186/ar3555
25. van den Bosch MHJ, van Lent PLEM, van der Kraan PM. Identifying effector molecules, cells, and cytokines of innate immunity in OA. *Osteoarthritis Cartilage*. 2020;28(5):532-543. doi:10.1016/j.joca.2020.01.016
26. Lieberthal J, Sambamurthy N, Scanzello CR. Inflammation in joint injury and post-traumatic osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(11):1825-1834. doi:10.1016/j.joca.2015.08.015
27. Collins JE, Katz JN, Dervan EE, Losina E. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage*. 2014;22(5):622-630. doi:10.1016/j.joca.2014.03.009
28. Duncan R, Peat G, Thomas E, et al. Does isolated patellofemoral osteoarthritis matter? *Osteoarthritis Cartilage*. 2009;17(9):1151-1155. doi:10.1016/j.joca.2009.03.016
29. Metcalfe D, Perry DC, Claireaux HA, et al. Does this patient have hip osteoarthritis? the rational clinical examination systematic review. *JAMA*. 2019;322(23):2323-2333. doi:10.1001/jama.2019.19413
30. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum*. 1991;34(5):505-514. doi:10.1002/art.1780340502
31. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum*. 1986;29(8):1039-1049. doi:10.1002/art.1780290816
32. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. *Clin Orthop Relat Res*. 2016;474(8):1886-1893. doi:10.1007/s11999-016-4732-4
33. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16(4):494-502. doi:10.1136/ard.16.4.494
34. Gold GE, Cicuttini F, Crema MD, et al. OARSI clinical trials recommendations: hip imaging in clinical trials in osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(5):716-731. doi:10.1016/j.joca.2015.03.004
35. Hunter DJ, Zhang W, Conaghan PG, et al. Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. *Osteoarthritis Cartilage*. 2011;19(5):557-588. doi:10.1016/j.joca.2010.10.029
36. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet*. 2011;377(9783):2115-2126. doi:10.1016/S0140-6736(11)60243-2
37. Podlipská J, Guermazi A, Lehenkari P, et al. Comparison of diagnostic performance of semi-quantitative knee ultrasound and knee radiography with MRI: Oulu Knee Osteoarthritis Study. *Sci Rep*. 2016;6:22365. doi:10.1038/srep22365
38. Fernandes L, Hagen KB, Bijlsma JW, et al; European League Against Rheumatism. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72(7):1125-1135. doi:10.1136/annrheumdis-2012-202745
39. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg*. 2013;21(9):571-576. doi:10.5435/JAAOS-21-09-571
40. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220-233. doi:10.1002/art.41142
41. Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2000;59(12):936-944. doi:10.1136/ard.59.12.936
42. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2003;62(12):1145-1155. doi:10.1136/ard.2003.011742
43. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2005;64(5):669-681. doi:10.1136/ard.2004.028886
44. Kovar PA, Allegante JP, MacKenzie CR, et al. Supervised fitness walking in patients with osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med*. 1992;116(7):529-534. doi:10.7326/0003-4819-116-7-529
45. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *JAMA*. 2013;310(12):1263-1273. doi:10.1001/jama.2013.277669
46. Reichenbach S, Felson DT, Hincapié CA, et al. Effect of biomechanical footwear on knee pain in people with knee osteoarthritis: the BIOTOK randomized clinical trial. *JAMA*. 2020;323(18):1802-1812. doi:10.1001/jama.2020.3565
47. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104(3):728-738.
48. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46-54. doi:10.7326/M14-1231
49. Lee C, Straus WL, Balshaw R, et al. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum*. 2004;51(5):746-754. doi:10.1002/art.20698
50. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2019;2(2):CD013273. doi:10.1002/14651858.CD013273
51. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ*. 2015;350:h1225. doi:10.1136/bmj.h1225
52. Zhu X, Wu D, Sang L, et al. Comparative effectiveness of glucosamine, chondroitin, acetaminophen or celecoxib for the treatment of knee and/or hip osteoarthritis: a network meta-analysis. *Clin Exp Rheumatol*. 2018;36(4):595-602.
53. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. *Pain Med*. 2012;13(6):740-753. doi:10.1111/j.1526-4637.2012.01394.x
54. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA*. 2017;317(19):1967-1975. doi:10.1001/jama.2017.5283
55. Deyle GD, Allen CS, Allison SC, et al. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. *N Engl J Med*. 2020;382(15):1420-1429. doi:10.1056/NEJMoA1905877
56. Conaghan PG, Hunter DJ, Cohen SB, et al. Effects of a single intra-articular injection of a microsphere formulation of triamcinolone acetonide on knee osteoarthritis pain: a double-blinded, randomized, placebo-controlled, multinational study. *J Bone Joint Surg Am*. 2018;100(8):666-677. doi:10.2106/JBJS.17.00154
57. Zeng C, Lane NE, Hunter DJ, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. *Osteoarthritis Cartilage*. 2019;27(6):855-862. doi:10.1016/j.joca.2019.01.007
58. Hochberg MC, Wohlreich M, Gaynor P, et al. Clinically relevant outcomes based on analysis of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis. *J Rheumatol*. 2012;39(2):352-358. doi:10.3899/jrheum.110307
59. Osani MC, Bannuru RR. Efficacy and safety of duloxetine in osteoarthritis: a systematic review

- and meta-analysis. *Korean J Intern Med.* 2019;34(5):966-973. doi:10.3904/kjim.2018.460
60. Enteshari-Moghaddam A, Azami A, Isazadehfahar K, et al. Efficacy of duloxetine and gabapentin in pain reduction in patients with knee osteoarthritis. *Clin Rheumatol.* 2019;38(10):2873-2880. doi:10.1007/s10067-019-04573-7
61. Fleischmann RM, Bliddal H, Blanco FJ, et al. A phase II trial of lutikizumab, an anti-interleukin-1 α / β dual variable domain immunoglobulin, in knee osteoarthritis patients with synovitis. *Arthritis Rheumatol.* 2019;71(7):1056-1069. doi:10.1002/art.40840
62. Kloppenburg M, Peterfy C, Haugen IK, et al. Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1 α and anti-interleukin-1 β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann Rheum Dis.* 2019;78(3):413-420. doi:10.1136/annrheumdis-2018-213336
63. Kloppenburg M, Ramonda R, Bobacz K, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.* 2018;77(12):1757-1764. doi:10.1136/annrheumdis-2018-213202
64. Schieker M, Conaghan PG, Mindeholm L, et al. Effects of interleukin-1 β inhibition on incident hip and knee replacement. *Ann Intern Med.* 2020;173(7):509-515. doi:10.7326/M20-0527
65. Yazici Y, McAlindon TE, Fleischmann R, et al. A novel Wnt pathway inhibitor, SMO4690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase I study. *Osteoarthritis Cartilage.* 2017;25(10):1598-1606. doi:10.1016/j.joca.2017.07.006
66. Hochberg MC, Guermazi A, Guehring H, et al. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. *JAMA.* 2019;322(14):1360-1370. doi:10.1001/jama.2019.14735
67. Conaghan PG, Bowes MA, Kingsbury SR, et al. Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis: a randomized controlled trial. *Ann Intern Med.* 2020;172(2):86-95. doi:10.7326/M19-0675
68. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project: overview of the National (Nationwide) Inpatient Sample (NIS). Accessed January 13, 2021. <https://www.hcup-us.ahrq.gov/nisoverview.jsp>
69. Katz JN, Losina E, Barrett J, et al. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States Medicare population. *J Bone Joint Surg Am.* 2001;83(11):1622-1629. doi:10.2106/00004623-200111000-00002
70. Memtsoudis SG, Della Valle AG, Besiculides MC, et al. Risk factors for perioperative mortality after lower extremity arthroplasty: a population-based study of 6,901,324 patient discharges. *J Arthroplasty.* 2010;25(1):19-26. doi:10.1016/j.arth.2008.11.010
71. Mahomed NN, Barrett J, Katz JN, et al. Epidemiology of total knee replacement in the United States Medicare population. *J Bone Joint Surg Am.* 2005;87(6):1222-1228.
72. Inacio MCS, Dillon MT, Miric A, et al. Mortality after total knee and total hip arthroplasty in a large integrated health care system. *Perm J.* 2017;21:16-171. doi:10.7812/TPP/16-171
73. Beswick AD, Wylde V, Goberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? a systematic review of prospective studies in unselected patients. *BMJ Open.* 2012;2(1):e000435. doi:10.1136/bmjopen-2011-000435
74. Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. *N Engl J Med.* 2015;373(17):1597-1606. doi:10.1056/NEJMoa1505467
75. Evans JT, Walker RW, Evans JP, et al. How long does a knee replacement last? a systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. *Lancet.* 2019;393(10172):655-663. doi:10.1016/S0140-6736(18)32531-5
76. Evans JT, Evans JP, Walker RW, et al. How long does a hip replacement last? a systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. *Lancet.* 2019;393(10172):647-654. doi:10.1016/S0140-6736(18)31665-9
77. Jasper LL, Jones CA, Mollins J, et al. Risk factors for revision of total knee arthroplasty: a scoping review. *BMC Musculoskelet Disord.* 2016;17:182-182. doi:10.1186/s12891-016-1025-8
78. Prokopetz JJ, Losina E, Bliss RL, et al. Risk factors for revision of primary total hip arthroplasty: a systematic review. *BMC Musculoskelet Disord.* 2012;13:251-251. doi:10.1186/1471-2474-13-251
79. Katz JN, Wright EA, Wright J, et al. Twelve-year risk of revision after primary total hip replacement in the US Medicare population. *J Bone Joint Surg Am.* 2012;94(20):1825-1832. doi:10.2106/JBJS.K.00569
80. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med.* 2002;347(2):81-88. doi:10.1056/NEJMoa013259
81. Katz JN, Wright J, Spindler KP, et al. Predictors and outcomes of crossover to surgery from physical therapy for meniscal tear and osteoarthritis: a randomized trial comparing physical therapy and surgery. *J Bone Joint Surg Am.* 2016;98(22):1890-1896. doi:10.2106/JBJS.15.01466
82. Katz JN, Brophy RH, Chaisson CE, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med.* 2013;368(18):1675-1684. doi:10.1056/NEJMoa1301408
83. Zhang W, Lyman S, Boutin-Foster C, et al. Racial and ethnic disparities in utilization rate, hospital volume, and perioperative outcomes after total knee arthroplasty. *J Bone Joint Surg Am.* 2016;98(15):1243-1252. doi:10.2106/JBJS.15.01009
84. Cavanaugh AM, Rauh MJ, Thompson CA, et al. Racial and ethnic disparities in utilization of total knee arthroplasty among older women. *Osteoarthritis Cartilage.* 2019;27(12):1746-1754. doi:10.1016/j.joca.2019.07.015
85. Mahomed NN, Barrett JA, Katz JN, et al. Rates and outcomes of primary and revision total hip replacement in the United States Medicare population. *J Bone Joint Surg Am.* 2003;85(1):27-32. doi:10.2106/00004623-200301000-00005
86. Hausmann LRM, Mor M, Hanusa BH, et al. The effect of patient race on total joint replacement recommendations and utilization in the orthopedic setting. *J Gen Intern Med.* 2010;25(9):982-988. doi:10.1007/s11606-010-1399-5
87. Byrne MM, Soucek J, Richardson M, Suarez-Almazor M. Racial/ethnic differences in preferences for total knee replacement surgery. *J Clin Epidemiol.* 2006;59(10):1078-1086. doi:10.1016/j.jclinepi.2006.01.010
88. Ibrahim SA, Siminoff LA, Burant CJ, Kwok CK. Understanding ethnic differences in the utilization of joint replacement for osteoarthritis: the role of patient-level factors. *Med Care.* 2002;40(1)(suppl):144-151. doi:10.1097/00005650-200201001-00006
89. Nwachukwu BU, Kenny AD, Losina E, et al. Complications for racial and ethnic minority groups after total hip and knee replacement: a review of the literature. *J Bone Joint Surg Am.* 2010;92(2):338-345. doi:10.2106/JBJS.I.00510
90. Deveza LA, Nelson AE, Loeser RF. Phenotypes of osteoarthritis: current state and future implications. *Clin Exp Rheumatol.* 2019;37(suppl 120)(5):64-72.
91. Nelson AE, Fang F, Arbeeve L, et al. A machine learning approach to knee osteoarthritis phenotyping: data from the FNHI Biomarkers Consortium. *Osteoarthritis Cartilage.* 2019;27(7):994-1001. doi:10.1016/j.joca.2018.12.027
92. Huang Z, Ding C, Li T, Yu SP. Current status and future prospects for disease modification in osteoarthritis. *Rheumatology (Oxford).* 2018;57(suppl 4):iv108-iv123. doi:10.1093/rheumatology/kex496
93. Jeon OH, Kim C, Laberge RM, et al. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. *Nat Med.* 2017;23(6):775-781. doi:10.1038/nm.4324
94. Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med.* 2010;363(16):1521-1531. doi:10.1056/NEJMoa0901510
95. Sanga P, Katz N, Polverean J, et al. Long-term safety and efficacy of fulranumab in patients with moderate-to-severe osteoarthritis pain: a phase II randomized, double-blind, placebo-controlled extension study. *Arthritis Rheumatol.* 2017;69(4):763-773. doi:10.1002/art.39943
96. Schnitzer TJ, Easton R, Pang S, et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: a randomized clinical trial. *JAMA.* 2019;322(1):37-48. doi:10.1001/jama.2019.8044
97. Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. *Osteoarthritis Cartilage.* 2015;23(suppl 1):S18-S21. doi:10.1016/j.joca.2014.10.005
98. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. *Arthritis Care Res (Hoboken).* 2011;63(8):1115-1125. doi:10.1002/acr.20492
99. Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SMA. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. *Arthritis Res Ther.* 2015;17(1):152. doi:10.1186/s13075-015-0670-x