JAMA | Review

Diagnosis and Treatment of Hip and Knee Osteoarthritis
A Review

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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.

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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 study[4] 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

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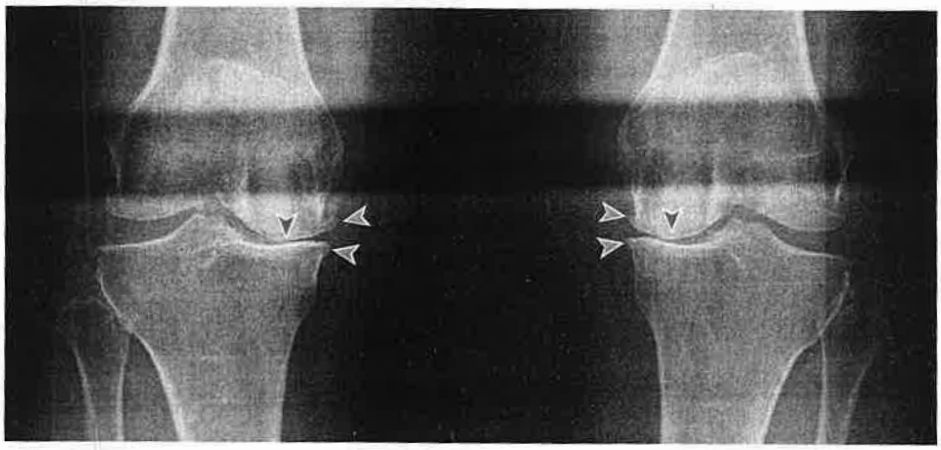
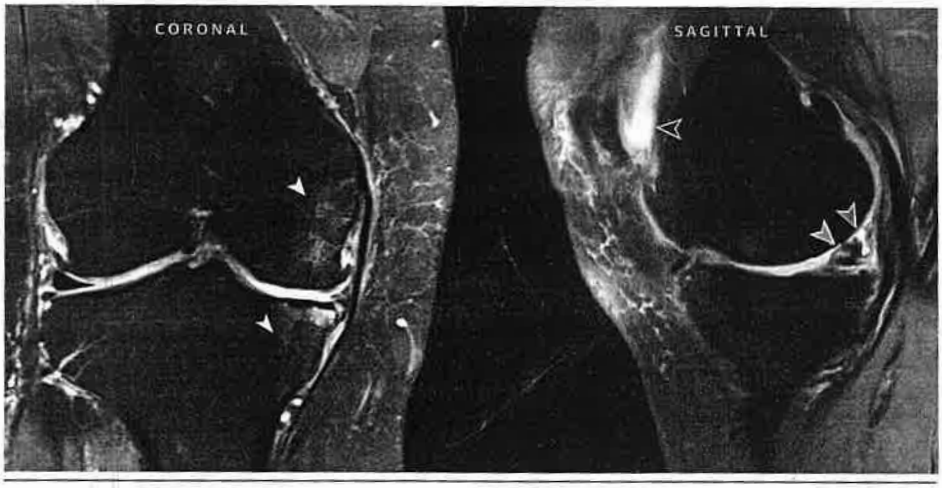
Figure 1. Imaging of Knee Osteoarthritis

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]

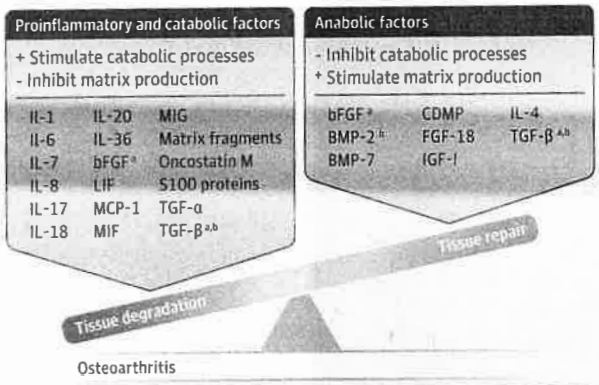
Methods

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 publications 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 1**A). 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,

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/μL 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]

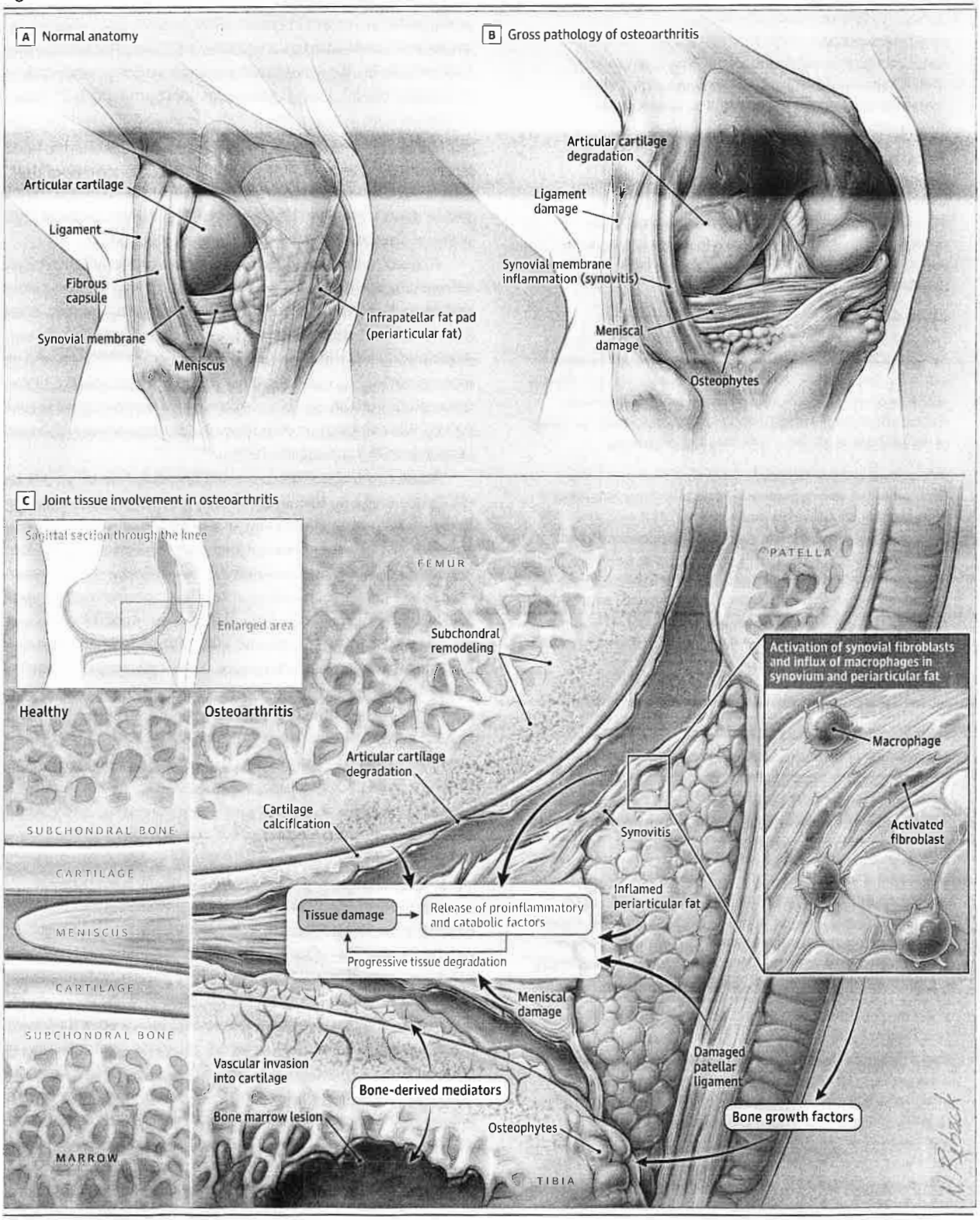
These data suggest that a presumptive diagnosis of hip or knee OA can be made on the basis of history and physical examination. Radiographs portray the severity of structural damage and improve specificity when osteophytes or joint space narrowing are present. Pathologic features and symptoms of OA can 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

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.

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	• 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	• 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	• 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	• 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	• 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]

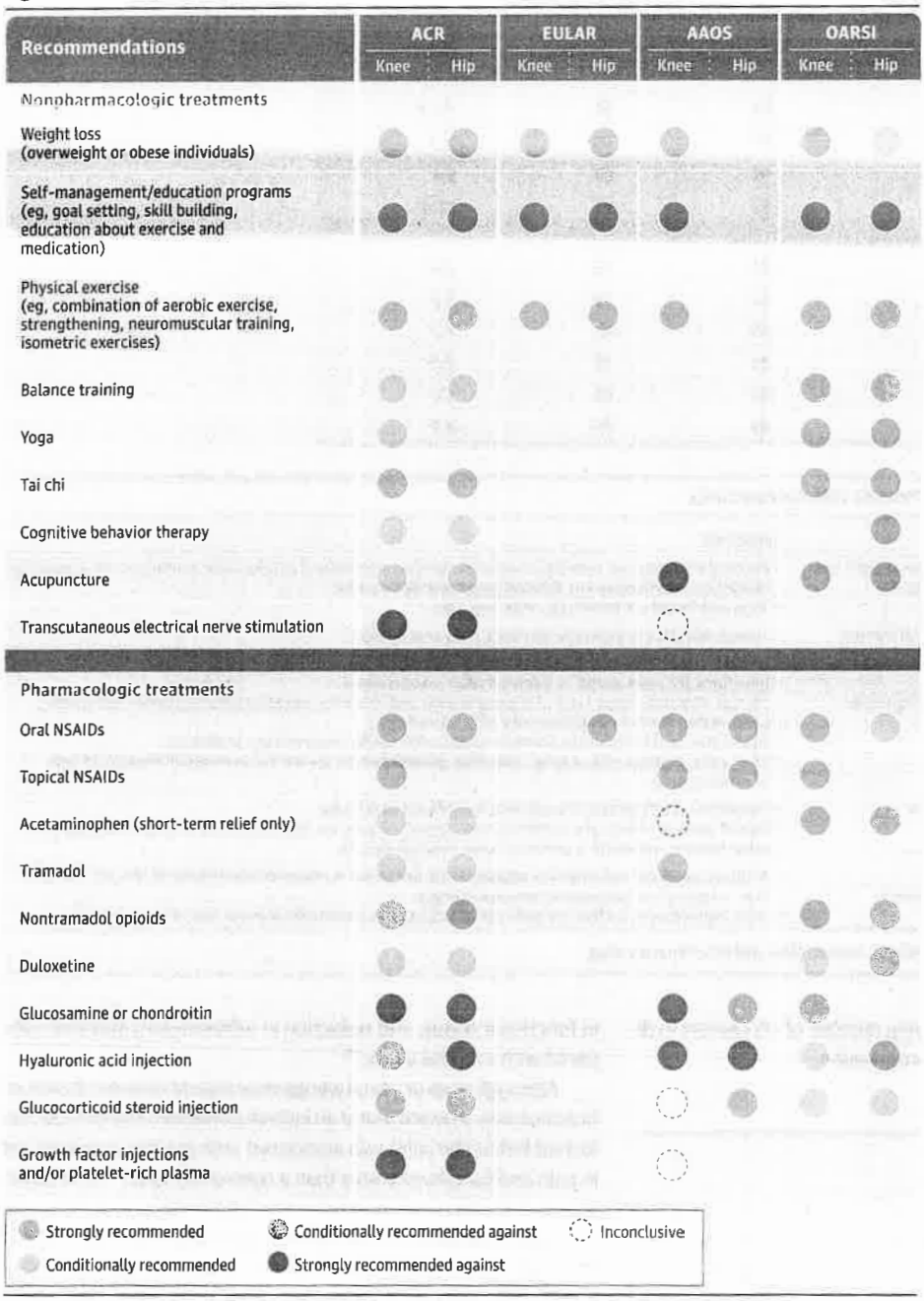
Structured exercise interventions that typically focus on strengthening of lower extremity muscles offer improvements in pain and functional status (SMD of 0.52 for knee OA and 0.34 for hip OA) (**Table 3**). A randomized clinical trial of a structured walking program showed a reduction in pain scores 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]



AAOS indicates American Academy of Orthopaedic Surgeons; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NSAID, nonsteroidal anti-inflammatory drug; OARSI, Osteoarthris 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 relieve 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 months[54] 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-1β, 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 inhibiton[65]; intra-articular injection of an anabolic growth factor, fibroblast growth factor 18[66]; 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 unicondylar 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 accounting 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.

Table 3. Standardized Mean Differences in Pain Score From Placebo-Controlled Trials of 4 to 12 Weeks' Duration[14]

	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.

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 activity, 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.

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FROM CONSUMER REPORTS

How to ease painful osteoarthritis

BY HALLIE LEVINE

As the years pass, many of us may begin to notice various aches and pains in our joints. One increasingly common cause of chronic discomfort is osteoarthritis, or OA, which is marked by a progressive loss of the cushioning material that keeps the ends of joints from rubbing together.

While this form of arthritis can get in the way of daily tasks and activities, it may have other bad effects: A study published in 2019 in the journal Osteoarthritis and Cartilage found that knee and hip OA was associated with an increased risk of dying from heart disease.

"OA may lead to increased sedentary behavior and as a result, increase a person's risk for other chronic issues, such as obesity, diabetes, high blood pressure, or heart disease due to decreased activity," says Eric K. Holder, assistant professor of clinical orthopedics and rehabilitation at Yale School of Medicine in New Haven, Conn. OA may also increase inflammation in the body, which itself is linked to heart disease. And a study published in 2020 in the Journal of the American Geriatrics Society found that the condition can lead to social isolation, which can also be harmful to health.

Good news: While many of the medications that are used for pain relief aren't recommended for regular use by older adults, a number of lifestyle and other nondrug treatments can help ease symptoms — and prevent OA from progressing, says Heidi Prather, a physiatrist at Hospital for Special Surgery in New York. Here's what experts advise.

ISTOCK

A woman practices tai chi. Many of the medications used for pain relief are not recommended for regular use by older adults, but a number of lifestyle strategies, including exercise, can help.

Why being calm matters

Reducing stress and getting a better night's sleep may not seem like they would help with OA. But some evidence suggests that they may. A study published in the journal PLOS One in 2020, for instance, found that people 50 and older who got six or fewer hours of sleep a night were 20 percent more likely to be diagnosed with OA than those who got between seven and eight hours. They were also about 30 percent more likely to experience significant joint pain.

"Sleep is crucial to pain perception," says Prather. Insufficient snooze time can reduce the levels of neurotransmitters — feel-good brain chemicals that can help blunt pain, she explains. Stress, for its part, can worsen sleep, thus altering the way that we perceive pain.

To address both issues, you can try a mindfulness technique such as meditation. One small study published in the journal Alternative and Complementary Therapies, for example, found that women with knee OA who meditated for 15 to 20 minutes twice a day for eight weeks reported significant improvements in pain and quality of life, and better knee function.

Dealing with mental health concerns such as depression and anxiety also is important. A study published in 2019 in the journal Pain found that people who reported symptoms of anxiety were 70 percent more likely to report knee pain over the next year. "There may be an association between these emotions and inflammation," Prather says. Talk with your doctor about therapies that can help.

Losing weight can help

If you are overweight, shedding as little as five to 10 pounds may help with pain and mobility. And a study published in 2021 in the International Journal of Obesity found that overweight and obese people who lost more than 7.5 percent of their body weight were less likely to require a total knee replacement compared with those who didn't lose weight or who gained weight.

Weight loss may also reduce your risk of Type 2 diabetes or, if you already have the condition, help you get it under control. "We know uncontrolled diabetes triggers inflammation that worsens osteoarthritis," says Eliana Cardozo, a sports medicine physician at Mount Sinai Hospital in New York.

Benefits of a plant-based diet

A 2018 study published in the journal Complementary Therapies in Medicine found that people who followed a plant-based eating style for eight weeks reported significant improvements in musculoskeletal pain — even if they did not lose weight. "A whole food, nutrient-dense diet that's low in processed products and sugar is key, since it helps reduce inflammation that contributes to pain," Holder says.

One good option: a Mediterranean-style diet, which is rich in produce, whole grains, seafood, beans and nuts. A high-sugar diet may negatively affect the gut microbiome, according to a study published in the journal PLOS One in 2021. And "your gut makes most of your body's serotonin, a brain chemical that boosts mood and makes it easier for you to tolerate pain," Prather says.

Exercise in the right ways

"In my opinion, exercise — including physical therapy — is the most important nonsurgical treatment out there to treat osteoarthritis," says orthopedic surgeon Timothy Gibson, medical director of the MemorialCare Joint Replacement Center at Orange Coast Medical Center in Fountain Valley, Calif. "It not only strengthens surrounding muscles, to take pressure off joints, but it improves overall function and provides a mental benefit, which can make coping with pain easier."

In terms of exercise, the most helpful for OA is a combination of aerobics, strength training, and flexibility exercises, says Elaine Husni, vice-chair of Rheumatic and Immunologic Diseases at Cleveland Clinic. But it's important to tailor workouts to your fitness level. "If a patient has been sedentary, I start them with water-based therapy, like pool aerobics," she says. "And once they tolerate that, they switch to low-impact, land-based therapy, like walking or biking."

Husni also recommends tai chi. A 2021 study published in the journal BMC Geriatrics found that older adults with knee OA who engaged in this gentle activity twice a week for 12 weeks performed much better on actions such as single leg stands than those who did not. Another good option is chair yoga. "It's especially good if you've been sedentary, because it takes away the fear of falling, and doesn't require as much core balance," Husni says.

If it hurts too much to exercise, ask your doctor whether a course of physical therapy might be warranted. A physical therapist can teach you how to strengthen the muscles around your joints with little or no pain, along with techniques to make daily activities easier, such as going up and down stairs.

What about medication?

For OA flare-ups, you can apply an over-the-counter topical to a painful joint. These include nonsteroidal anti-inflammatories such as Voltaren, and products with capsaicin, such as Zostrix.

For more relief, you may be able to use OTCs such as ibuprofen (Motrin IB, generic) for a short time if you have well-controlled blood pressure, and a healthy liver and kidney, Husni says. Ask your doctor. Otherwise, acetaminophen (Tylenol, generic) may be best.

There are also injectables: steroids, hyaluronic acid and platelet-rich plasma (PRP) — an experimental treatment that uses a patient's own platelets.

Hyaluronic acid, similar to a substance in the joints, may work for some people, but American Academy of Orthopaedic Surgeons guidelines do not advise it for routine use in OA. PRP has shown some promise for tendon, muscle, and ligament injuries in younger people, but not for moderate to severe OA, Husni says.

"For some people, a certain injection can help their pain for a while," says Cardozo, who also advises an individualized approach based on factors like the degree of arthritis.

ORIGINAL ARTICLE

Physical Therapy versus Glucocorticoid Injection for Osteoarthritis of the Knee

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ABSTRACT

BACKGROUND

Both physical therapy and intraarticular injections of glucocorticoids have been shown to confer clinical benefit with respect to osteoarthritis of the knee. Whether the short-term and long-term effectiveness for relieving pain and improving physical function differ between these two therapies is uncertain.

METHODS

We conducted a randomized trial to compare physical therapy with glucocorticoid injection in the primary care setting in the U.S. Military Health System. Patients with osteoarthritis in one or both knees were randomly assigned in a 1:1 ratio to receive a glucocorticoid injection or to undergo physical therapy. The primary outcome was the total score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 1 year (scores range from 0 to 240, with higher scores indicating worse pain, function, and stiffness). The secondary outcomes were the time needed to complete the Alternate Step Test, the time needed to complete the Timed Up and Go test, and the score on the Global Rating of Change scale, all assessed at 1 year.

RESULTS

We enrolled 156 patients with a mean age of 56 years; 78 patients were assigned to each group. Baseline characteristics, including severity of pain and level of disability, were similar in the two groups. The mean (±SD) baseline WOMAC scores were 108.8±47.1 in the glucocorticoid injection group and 107.1±42.4 in the physical therapy group. At 1 year, the mean scores were 55.8±53.8 and 37.0±30.7, respectively (mean between-group difference, 18.8 points; 95% confidence interval, 5.0 to 32.6), a finding favoring physical therapy. Changes in secondary outcomes were in the same direction as those of the primary outcome. One patient fainted while receiving a glucocorticoid injection.

CONCLUSIONS

Patients with osteoarthritis of the knee who underwent physical therapy had less pain and functional disability at 1 year than patients who received an intraarticular glucocorticoid injection. (ClinicalTrials.gov number, NCT01427153.)

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OSTEOARTHRITIS OF THE KNEE IS A leading cause of disability.[1] Current management is typically limited to the treatment of symptoms until late stages of arthritis lead to knee replacement.[2] Intraarticular glucocorticoid injections are commonly used as a primary treatment for osteoarthritis of the knee,[3] but there are conflicting reports regarding the extent and duration of the relief of symptoms with this therapy.[4-6] Complications from these injections occur infrequently but include joint infection,[7] accelerated degradation of articular cartilage,[8] and subchondral insufficiency fractures.[9] Clinical practice guidelines vary regarding the use of glucocorticoid injections for osteoarthritis of the knee,[10-12] with a recent clinical practice guideline providing the highest level of endorsement ("strongly recommended") for intraarticular glucocorticoid injections.[13] A study that used data from Humana on more than 1 million patients from 2007 through 2015 showed that 38% of the patients with osteoarthritis of the knee received a glucocorticoid injection.[10] In two other large population cohorts, 50%[14] and 43.5%[3] of patients received a glucocorticoid injection before total knee replacement.

Some clinical trials of treatments for osteoarthritis of the knee have suggested that physical therapy confers short-term and long-term relief of symptoms, functional improvement, and a decreased need for pain medications, including opioids.[15-20] However, despite some guideline recommendations for physical therapy and lifestyle changes as primary treatments, the use of physical therapy for osteoarthritis of the knee declined between 2007 and 2015.[21] In one large claims database analysis, four times as many patients with osteoarthritis of the knee received a glucocorticoid injection as received physical therapy before total knee replacement.[3] In the U.S. Military Health System, patients who were referred for therapy within 30 days after an initial diagnosis of osteoarthritis of the knee were more likely to be referred for glucocorticoid injection than for physical therapy (51% vs. 29%), and only 13% received both.[22] No clinical practice guidelines recommend using these two treatments together. One trial determined that glucocorticoid injection added to physical therapy provided no further benefit.[23] Strategies such as the use of manual physical therapy to improve movement and reduce pain that occurs during exercise and daily activities may not be well understood. A recent clinical practice guideline conditionally recommended against manual physical therapy either with or without exercise.[13] We performed a trial to compare the effectiveness of glucocorticoid injection with that of physical therapy in patients with osteoarthritis of the knee.

METHODS

PATIENTS

Patients were beneficiaries of the Military Health System and were active-duty or retired service members or their family members. Eligible patients were 38 years of age or older and presented to one of two large military hospitals from October 2012 through May 2017. Patients received treatment at a participating clinic at Madigan Army Medical Center, Tacoma, Washington (one physical therapy clinic and one orthopedic clinic) or Brooke Army Medical Center, San Antonio, Texas (one physical therapy clinic, one rheumatology clinic, and one orthopedic clinic).

Eligible patients met the criteria of the American College of Rheumatology clinical classification for osteoarthritis of the knee[24] and had radiographic evidence of osteoarthritis (weight-bearing views) assessed as Kellgren–Lawrence grade 1 (doubtful narrowing, possible osteophytic lipping) to grade 4 (highest Kellgren–Lawrence grade, indicating large osteophytes and marked narrowing of joint space).[25] We excluded patients who had received a glucocorticoid injection or had undergone physical therapy for knee pain in the previous 12 months or who had no radiographic evidence of osteoarthritis (Kellgren–Lawrence grade 0). Detailed inclusion and exclusion criteria are provided in the protocol[26] (available with the full text of this article at NEJM.org).

TRIAL OVERSIGHT

The institutional review board at Madigan Army Medical Center approved the protocol. The authors vouch for the accuracy and completeness of the data, for the fidelity of the trial to the protocol, and for full reporting of adverse events.

TRIAL PROCEDURES

Patients were informed of the trial during an initial primary care or physical therapy visit. Research coordinators provided each patient with information about the trial, obtained written informed consent, and coordinated entry into the trial. Before randomization, we obtained demographic information and all baseline measures and provided education, based on current guidelines, that addressed the relationship between osteoarthritis of the knee and physical activity, nutrition, and obesity.[27]

Patients were assigned in a 1:1 ratio to undergo physical therapy or to receive a glucocorticoid injection in the joint (the trial design did not include a placebo injection). Assignment to treatment group was determined according to sequentially numbered labels prepared with the use of an electronic random number generator. These labels were placed inside corresponding numbered opaque envelopes and mailed to each site. Research assistants who were not investigators performed outcome assessments and were unaware of the trial-group assignments. Patients received guidance during each appointment-reminder telephone call and from the assistants at the beginning of each data-collection session about not revealing or discussing anything that would disclose their treatment to the assistants who performed the outcome assessments. At each time point during which data were collected, the assistants answered a yes-or-no question that determined whether blinding had been maintained; they also reminded patients to complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Global Rating of Change scale questionnaires regarding the knee that was identified as worse with respect to pain and physical function at baseline. Patients with symptoms in both knees received treatment in both knees, but trial outcomes were assessed only in the knee with worse symptoms at baseline.

GLUCOCORTICOID INJECTIONS

Orthopedists or rheumatologists performed the intraarticular injections according to local standards. One of the orthopedic providers who performed injections was a trial investigator. Patients received an injection in one or both knees of 1 ml of triamcinolone acetonide (40 mg per milliliter)[28] and 7 ml of 1% lidocaine with the use of sterile technique. The same treating providers examined patients again at 4 months and 9 months to discuss the continued plan of care, including the appropriateness of additional glucocorticoid injections. Patients could receive up to three injections over the 1-year trial period, at the discretion of the clinician.

PHYSICAL THERAPY

The physical therapy intervention, which is described in the protocol,[26] included instructions and images for exercises, joint mobilizations, and the clinical reasoning underlying the priorities, dosing, and progression of treatment. During a typical clinical session, the physical therapist would implement hands-on, manual techniques immediately before the patient performed reinforcing exercises to help the patient perform the movements with little or no pain. For example, if a patient could not fully extend or flex the knee, or those movements were painful, the physical therapist would use a hands-on, passive mobilizing technique to repeatedly move the knee to reduce stiffness while altering the mechanics of the technique to avoid pain. The patient would then perform repeated active knee movements in the same direction. Similarly, if muscles around the knee were tight, the physical therapist would perform manual muscle stretching before the patient would perform the same stretches. A strategy of hands-on, passive movement followed by reinforcing exercise in a single session has been shown to improve knee extension in patients with osteoarthritis.[29] Patients underwent up to eight treatment sessions over the initial 4-to-6-week period; the patient could attend an additional one to three sessions at the time of the 4-month and 9-month reassessments if that plan of care was agreed on by the physical therapist and the patient. The five treating physical therapists, who were investigators in this trial, were board certified in orthopedic physical therapy and fellowship-trained in orthopedic manual physical therapy.

ASSESSMENTS AND OUTCOMES

We assessed outcome measures for pain, physical function, and global assessment according to the recommendations for clinical trials of the Outcome Measures in Rheumatology–Osteoarthritis Research Society International.[30] The primary outcome was the total WOMAC score at

1 year. We used WOMAC, version 3.1, which contains 24 items and is composed of three subscales: pain (5 questions), physical function (17 questions), and stiffness (2 questions). Each item is rated on a scale of 0 to 10 (with higher scores indicating worse pain, function, and stiffness), and total scores range from 0 to 240. Secondary outcomes were the score on the 15-point Global Rating of Change scale (scores range from –7 to +7, with higher positive values indicating more improvement and lower negative values indicating worsening symptoms), the 1-year cost of knee-related health care utilization, and the results of two functional tasks (the Timed Up and Go test[31] and the Alternate Step Test,[32] both measured in seconds to complete the task, with a mean of three trials for each functional measure).

The minimal clinically important difference for the total WOMAC score has been reported to be a 12% or 16% improvement from baseline.[33,34] The Global Rating of Change scale measures perceived improvement, and a score of +3 ("somewhat better") or higher is considered to be clinically meaningful.[35] There is no published minimal clinically important difference for the Alternate Step Test. Estimates of clinically important improvement for the Timed Up and Go test range from 0.8 to 1.2 seconds.[36]

Data regarding health care utilization were obtained from the Military Health System Data Repository, which captures person-level data for all outpatient and inpatient medical visits to military and civilian hospitals. We identified all medical visits and associated costs for care with a code for a knee diagnosis or a knee procedure in the entire 1-year trial period, starting from the day of enrollment and including all trial-related care. No formal cost-effectiveness analysis was conducted, but descriptive cost values for each group are provided in the Supplementary Appendix, available at NEJM.org.

ADVERSE EVENTS

In addition to serious adverse events of death, infection, and fracture, we defined an adverse event as a persistent worsening of symptoms resulting in additional treatment outside the trial.[26] We asked patients at every follow-up to report any complications, signs, or symptoms they perceived as an adverse outcome related to their treatment. We also recorded any additional care and examined claims data in the Military Health System Data Repository to identify and validate reported additional care, including emergency department visits.

STATISTICAL ANALYSIS

We calculated that a sample size of 138 patients would provide the trial with 80% power, at a two-sided alpha level of 0.05, to detect an interaction of time with treatment group, assuming that group means would be equal at baseline, that there would be a difference between groups of 12 percentage points in mean WOMAC scores at the first post-treatment assessment, and that this difference would be unchanged at each subsequent assessment.[34] The calculation of the group mean WOMAC score was based on five repeated measurements, a common standard deviation of 46.8, a mean correlation between repeated measures of 0.681, and a nonsphericity correction factor of 0.890 — values consistent with data from previous trials.[16,17] The sample-size calculation was performed with the use of G*Power software, version 3.1.2.[37] We added approximately 10% more participants to account for potential loss to follow-up, resulting in a final enrollment goal of 156 participants (78 per group).

All analyses were performed with the use of the intention-to-treat approach. We had planned to use a linear mixed-effects model for analyses, but after the discovery of significant positive skewness in the distributions of scores on the continuous scales, we used a log-linear mixed-effects model[38] to analyze the measurements on those scales. The model included treatment, time, and the interaction of treatment with time as fixed effects and patient-specific random intercepts. Outcome analyses are reported as least-squares means and 95% confidence intervals, including the mean differences between groups. There were no prespecified adjustments for multiple comparisons, but P values and their corresponding 95% confidence intervals for post hoc pairwise comparisons for all outcomes are reported with Bonferroni adjustment. We prespecified the use of our statistical model as the primary plan for handling missing data, and we imputed missing values post hoc with the use of the Markov chain Monte Carlo method with 20 imputations in sensitivity analyses.[39] Categorical outcomes for dichotomized variables at 1 year were analyzed with two-by-two contingency tables to determine relative risk, absolute and relative

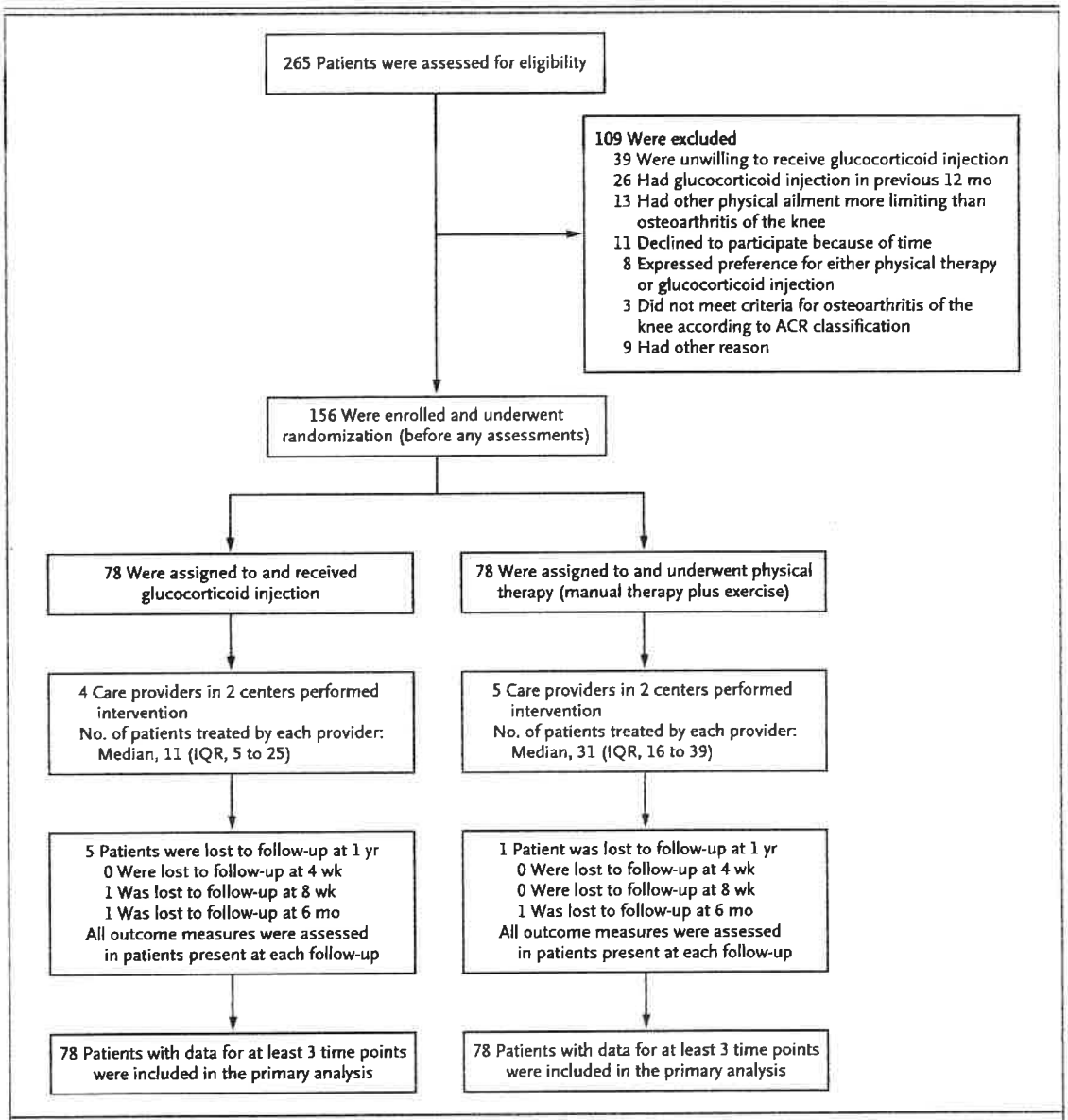

Figure 1. Trial Enrollment and Follow-up.

ACR denotes American College of Rheumatology, and IQR interquartile range.

risk reductions, and the numbers needed to treat, with failure to have a clinically meaningful benefit as the event of interest. We planned for two large military hospitals to participate but were able to enroll only four participants at one of the hospitals. For this reason, we did not adjust our model for trial site. We compared the mean costs between groups with the use of a generalized linear model with a log link. We used SPSS software, version 24.0 (IBM), for all analyses. Data were missing for 1.4% of all values and for 7% of data on primary and secondary outcomes. Every participant had primary outcome data available for at least three time points. The statistical analysis plan is available with the protocol.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Total Cohort (N=156)	Glucocorticoid Injection (N=78)	Physical Therapy (N=78)
Age — yr	56.1±8.7	56.0±8.2	56.3±9.2
Female sex — no. (%)	75 (48.1)	38 (48.7)	37 (47.4)
Body-mass index	31.5±5.6	31.6±6.1	31.4±5.1
Beneficiary category — no. (%)			
Active duty	36 (23.1)	19 (24.4)	17 (21.8)
Army Reserve or National Guard	5 (3.2)	1 (1.3)	4 (5.1)
Retired service member	54 (34.6)	26 (33.3)	28 (35.9)
Family member	61 (39.1)	32 (41.0)	29 (37.2)
Smoker — no. (%)	8 (5.1)	3 (3.8)	5 (6.4)
Duration of symptoms — mo†	92.5±107.2	85.0±89.2	100.0±122.7
Baseline symptoms — no./total no. (%)			
Knee swelling	98/149 (65.8)	46/76 (60.5)	52/73 (71.2)
Knee giving way	80/149 (53.7)	39/76 (51.3)	41/73 (56.2)
Knee locking	44/149 (29.5)	21/76 (27.6)	23/73 (31.5)
More symptomatic knee — no. (%)			
Right knee	72 (46.2)	32 (41.0)	40 (51.3)
Left knee	70 (44.9)	39 (50.0)	31 (39.7)
Equal	14 (9.0)	7 (9.0)	7 (9.0)
Right-hand dominant — no./total no. (%)	137/154 (89.0)	69/76 (90.8)	68/78 (87.2)
Symptoms in both knees — no./total no. (%)	98/154 (63.6)	49/76 (64.5)	49/78 (62.8)
Kellgren–Lawrence grade — no. (%)‡			
1	6 (3.8)	1 (1.3)	5 (6.4)
2	68 (43.6)	42 (53.8)	26 (33.3)
3	59 (37.8)	25 (32.1)	34 (43.6)
4	23 (14.7)	10 (12.8)	13 (16.7)
Knee pain affects sleep — no./total no. (%)			
No	38/155 (24.5)	19/77 (24.7)	19/78 (24.4)
A little, but can sleep through the night	113/155 (72.9)	56/77 (72.7)	57/78 (73.1)
Cannot sleep because of pain	4/155 (2.6)	2/77 (2.6)	2/78 (2.6)
Baseline measures			
WOMAC total score§	108.0±44.7	108.8±47.1	107.1±42.4
Time to complete Alternate Step Test — sec	11.3±2.8	11.7±3.0	10.9±2.5
Time to complete Timed Up and Go test — sec	9.7±2.8	9.9±3.0	9.4±2.5

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Duration of symptoms was reported by the patient.
‡ Grades on the Kellgren–Lawrence scale range from 0 (no radiographic evidence of osteoarthritis) to 4 (large osteophytes, marked narrowing of joint space).
§ The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores range from 0 to 240, with higher scores indicating worse pain, function, and stiffness.

Table 2. Primary and Secondary Outcomes at 1 Year.*

Outcome	Glucocorticoid Injection	Physical Therapy	Mean Between-Group Difference (95% CI)
Primary outcome: total WOMAC score — least-squares mean (95% CI)	55.8 (45.0–69.1)	37.0 (30.8–44.5)	18.8 (5.0–32.6)†
Secondary outcomes			
Median Global Rating of Change score (IQR)‡	+4 (0.5–6.0)	+5 (3.3–6.0)	
Least-squares mean time to complete Alternate Step Test — sec (95% CI)	9.0 (8.5–9.5)	8.0 (7.6–8.4)	1.0 (0.3–1.6)§
Least-squares mean time to complete Timed Up and Go test — sec (95% CI)	8.1 (7.7–8.6)	7.3 (6.8–7.7)	0.9 (0.3–1.5)¶

* All 156 patients were included in the analyses. The 95% confidence intervals and reported P values were adjusted with the use of Bonferroni correction for multiple comparisons.
† The between-group difference is the difference in points (P=0.008).
‡ Scores on the Global Rating of Change scale range from −7 to +7, with higher positive values indicating more improvement and lower negative values indicating worsening symptoms; a score of +4 indicates "moderately better," and a score of +5 "quite a bit better." A total of 50 patients in the glucocorticoid injection group and 67 in the physical therapy group had a score of at least +3.
§ The between-group difference is the difference in seconds (P=0.003).
¶ The between-group difference is the difference in seconds (P=0.005).

RESULTS

PATIENTS

From October 2012 through May 2017, we screened 265 patients who met diagnostic criteria for osteoarthritis of the knee and enrolled 156 patients; the mean age of the patients was 56.1 years, 48% were women, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) of the entire cohort was 31.5. The primary reasons for exclusion were unwillingness to receive a glucocorticoid injection and receipt of a glucocorticoid injection in the previous 12 months (Fig. 1). A total of 78 patients were randomly assigned to each group. Patients in the glucocorticoid injection group received a mean of 2.6 injections (range, 1 to 4). Patients in the physical therapy group attended a mean of 11.8 treatment visits (range, 4 to 22) (Table S9 in the Supplementary Appendix). Baseline demographic and clinical characteristics were similar in the two groups, except for radiographic severity of osteoarthritis measured according to the Kellgren–Lawrence scale[25] — more patients in the physical therapy group than in the glucocorticoid injection group had a Kellgren–Lawrence grade of 3 or 4 (Table 1). Seven patients (9%) in the physical therapy group also received a glucocorticoid injection; 14 patients (18%) in the glucocorticoid injection group also received physical therapy.

Assessors became aware of the trial-group assignment during 11 of 616 postbaseline data-gathering sessions (for 6 patients in the physical therapy group and 5 in the glucocorticoid injection group) (Table S6). The mean cost for all knee-related medical care during the 1-year trial period was similar in the two groups ($2,113 in the glucocorticoid injection group and $2,131 in the physical therapy group) (Table S5). Some patients in each group sought additional care outside the trial. Four patients in the glucocorticoid group had surgery (3 underwent total knee replacements and 1 underwent arthroscopy) (Table S8).

PRIMARY OUTCOME

The mean (±SD) WOMAC scores at 1 year were 55.8±53.8 in the glucocorticoid injection group and 37.0±30.7 in the physical therapy group (mean between-group difference, 18.8 points; 95% confidence interval [CI], 5.0 to 32.6; P=0.008) (Table 2 and Fig. 2). (The least-squares mean WOMAC scores at all trial time points are provided in Table S1 and Fig. S1.) In a prespecified analysis, 8 patients (10.3%) in the physical therapy group, as compared with 20 (25.6%) in the glucocorticoid injection group, did not have an improvement from baseline of at least 12% (the minimal clinically important difference[34]) in the WOMAC score at 1 year (Table S3). The overall direction of results for the primary outcome remained unchanged in five post hoc

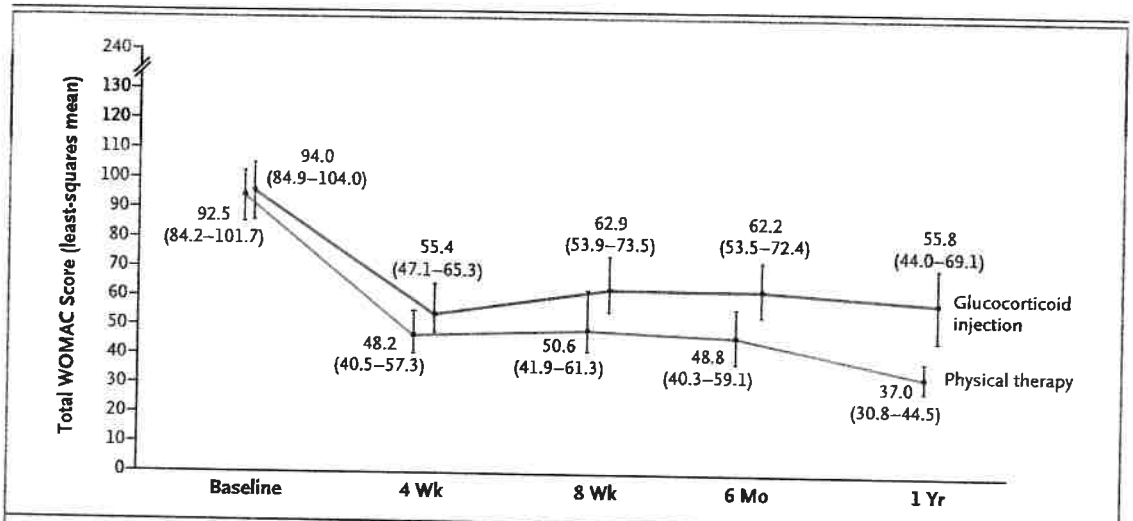

Figure 2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Total Scores over the 12-Month Follow-up Period.

WOMAC total scores range from 0 to 240, with higher scores indicating worse pain, function, and stiffness. The values in parentheses are 95% confidence intervals (also indicated by the I bars). All 156 participants (78 per group) were included in the analysis.

sensitivity analyses — those performed with imputation for missing data, with exclusion of 6 participants without WOMAC data at 1 year, with adjustment for differences in radiographic severity and duration of symptoms at baseline, with exclusion of 7 patients in the physical therapy group who received a glucocorticoid injection, and with exclusion of 14 patients in the injection group who received physical therapy (Table S4).

SECONDARY OUTCOMES

At 1 year, the median score on the Global Rating of Change scale was +5 ("quite a bit better") in the physical therapy group and +4 ("moderately better") in the glucocorticoid injection group (Table 2). A total of 11 patients (14.1%) in the physical therapy group, as compared with 26 (33.3%) in the glucocorticoid injection group, did not have a score on the Global Rating of Change scale of +3 or higher at 1 year (relative risk, 0.42; 95% CI, 0.23 to 0.80) (Table S2 and Fig. S2). Data were imputed for 6 patients who had missing data. The mean difference between groups at 1 year for the Alternate Step Test was 1.0 second (95% CI, 0.3 to 1.6) and for the Timed Up and Go test, 0.9 seconds (95% CI, 0.3 to 1.5); patients in the physical therapy group performed better (had lower mean times) on both tests than patients in the glucocorticoid injection group (Bonferroni adjustment of 95% confidence intervals are provided in Table 2, and no definite inferences can be made because this was not the prespecified method of analysis). One patient in the glucocorticoid group fainted while receiving an injection; there were no other adverse events.

DISCUSSION

This trial comparing physical therapy with glucocorticoid injection in symptomatic patients with clinical[40] and radiographic[25] evidence of osteoarthritis in one or both knees showed that physical therapy was more effective than glucocorticoid injections in leading to improved outcomes at 1 year, as assessed by the total WOMAC score. Secondary outcomes that measured functional tasks and patient assessment of improvement also favored physical therapy. The median score on the Global Rating of Change scale in both groups was above the clinically meaningful threshold of perceived improvement; however, 18 patients (23%) in the glucocorticoid group and 7 (9%) in the physical therapy group reported no perceived improvement or reported worsening symptoms at 1 year. Health care costs over the 1-year trial period were similar in the two groups, but no formal comparisons were made between groups.

Previous studies of physical therapy for osteo-

arthritis of the knee, with treatment limited to 4 weeks, showed large short-term benefits exceeding minimal clinically important difference thresholds for the change from baseline in WOMAC score, and the benefits persisted to 1 year.[16,17] However, by 1 year, mean WOMAC scores in these studies were regressing toward baseline values. In our trial, we found a similar effect size for short-term improvement with physical therapy but an even greater reduction from baseline in the mean WOMAC score at 1 year. This difference seen in our trial at 1 year may have been the result of the educational sessions, additional provider contact at 4 months and 9 months, and the use of interim treatment visits as needed.[41,42]

The within-group effect size for glucocorticoid injection in this trial was greater than effect sizes reported in other clinical trials.[4,5] This finding is potentially explained by the educational sessions, the follow-up visits with clinicians, which provided the opportunity for additional injections throughout the 1-year trial period, and the additional care sought by some patients outside the trial protocol.

The results of our trial are consistent with those of previous trials,[16,17] which suggests that the short-term improvement expected with glucocorticoid injection can also be seen with physical therapy; however, treatment effects of physical therapy persist for a year. Glucocorticoid injections are used in clinical practice more frequently than physical therapy.[3,10,14]

There are limitations to this trial. First, patients assigned to physical therapy had more visits with a health care provider than patients in the glucocorticoid group, which resulted in more provider contact time. Second, 18% of patients assigned to glucocorticoid injections also received physical therapy treatment, four patients had surgery, and four had more than three injections (the protocol allowed for up to three injections); in addition, 9% of patients assigned to physical therapy also received a glucocorticoid injection. These additional interventions may have contributed to the observed benefit within and between groups. Third, there was a higher proportion of patients with severe arthritis (Kellgren–Lawrence grades 3 and 4)[25] in the physical therapy group than in the glucocorticoid injection group. Fourth, this trial compared the two treatments as independent interventions and cannot be generalized to cases in which both interventions are used concurrently. Fifth, it was not possible to conceal trial-group assignment from patients or providers. Finally, most patients in this trial were referred directly by primary care physicians; however, approximately one third were identified during an initial physical therapy visit. This method of recruitment may have biased the trial sample toward patients more likely to benefit from physical therapy and may have influenced patients' perception of the interventions; however, patient expectations regarding the benefit of the assigned treatment were similar in the two groups, and all screened patients who wanted only physical therapy were excluded (Table S7).

In conclusion, physical therapy for osteoarthritis of the knee resulted in better absolute scores on scales of pain and physical function than glucocorticoid injection at 1 year.

The views expressed here are those of the authors and do not reflect the official policy or position of Madigan Army Medical Center, Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Air Force, the Department of the Army, the Department of Defense, or the U.S. government.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Osteoarthritis: the resultant change in the condition of a joints due to mechanical (primary) or inflammatory (secondary) factors

1. Primary osteoarthritis – cartilage degradation
   a. Chondrocyte dysfunction
   b. Loss and inability to retain water
   c. Cartilage stiffness and loss of resiliency

Contributing factors

   a. Age
   b. Genetics
   c. Injury
   d. Congenital (hip dysplasia)
   e. Inherited disorders of connective tissue – Marfans syndrome, Ehlers Danlos,ligamentous laxity)

Common joint targets

   a. Hands and feet (knobby knuckles and bunions)
   b. Knees (meniscal cartilage v. hyaline cartilage)
   c. Hips (old microfractures v. acetabular (ball and socket) changes
   d. Spine (neck and lower back) – disc space narrowing, facet joint degeneration

2. Secondary osteoarthritis – the influence of underlying extra-articular phenomena that lead to cartilage destruction and joint damage

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DOI: 10.1056/NEJMe2000239

Physical Therapy before the Needle for Osteoarthritis of the Knee

Kim L. Bennell, Ph.D., and David J. Hunter, Ph.D.

Clinical guidelines for the treatment of osteoarthritis of the knee emphasize education, exercise, and (if appropriate) weight loss, rather than the use of drugs or surgery.[1,2] However, a survey conducted in four European countries showed that these treatments were recommended to fewer than half the patients; stronger painkillers were recommended in 52% of patients, and 36% were referred for surgery.[3] Intraarticular glucocorticoid injections are commonly used to treat osteoarthritis of the knee, partly because they are easy to administer, they involve fewer visits than other treatments, and patient adherence is not an issue. But benefits may be short-lived, and adverse effects on the joint have been reported, including a small increase in loss of cartilage volume of uncertain clinical relevance.[4] In contrast, physical therapy, including exercise, is used less frequently than glucocorticoid injections, and although physical therapy requires patient participation and investment of time, it is noninvasive, has negligible adverse effects, and may have longer-lasting benefits than glucocorticoid injections.

Few trials have directly compared different treatments for osteoarthritis of the knee. In this issue of the *Journal*, Deyle and colleagues[5] report the results of a pragmatic, randomized, controlled trial conducted predominantly in one military hospital in the United States. A total of 156 outpatients with osteoarthritis of the knee were assigned to undergo physical therapy or to receive intraarticular glucocorticoid injections. Outcomes were assessed at 12 months. It was not possible to conceal treatment assignments from patients or providers, and placebo injections were not included in the trial design.

Over the 12-month trial period, patients in the physical therapy group attended a mean of 11.8 treatment visits (range, 4 to 22), at which they received manual physical therapy and instruction on home exercise. The glucocorticoid injection group received a mean of 2.6 injections (range, 1 to 4) of triamcinolone acetonide. The primary outcome was the total score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; scores range from 0 to 240, with higher scores indicating worse pain, function, and stiffness). Patients in the physical therapy group had less pain and functional disability at 1 year than patients in the glucocorticoid injection group. Although the magnitude of the absolute between-group difference in total WOMAC score (18.8 points) was small, 8 of 78 patients (10.3%) in the physical therapy group, as compared with 20 of 78 (25.6%) in the glucocorticoid injection group, did not have an improvement from baseline of at least 12% (the minimal clinically important difference) in the WOMAC score. Secondary outcomes measuring functional tasks and patient assessment of improvement, as well as sensitivity analyses, were in the same direction as the primary outcome, with the results favoring physical therapy. The results of the trial contrast with recent recommendations from some medical and research societies against manual therapy for osteoarthritis of the knee.[1,2]

There are several issues regarding the trial that are worth considering. First, patients in the physical therapy group had considerably greater contact time with clinicians than patients in the glucocorticoid injection group. This may have accentuated placebo effects and the therapeutic

Osteoarthritis: the resultant change in the condition of a joints due to mechanical (primary) or inflammatory (secondary) factors

1. Primary osteoarthritis – cartilage degradation
   a. Chondrocyte dysfunction
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   c. Cartilage stiffness and loss of resiliency

Contributing factors
   a. Age
   b. Genetics
   c. Injury
   d. Congenital (hip dysplasia)
   e. Inherited disorders of connective tissue – Marfans syndrome, Ehlers Danlos,ligamentous laxity)

Common joint targets
   a. Hands and feet (knobby knuckles and bunions)
   b. Knees (meniscal cartilage v. hyaline cartilage)
   c. Hips (old microfractures v. acetabular (ball and socket) changes
   d. Spine (neck and lower back) – disc space narrowing, facet joint degeneration

2. Secondary osteoarthritis – the influence of underlying extra-articular phenomena that lead to cartilage destruction and joint damage

alliance, which is a predictor of better outcomes. Second, the results may reflect a lack of long-term efficacy of injections (at 12 months, when the primary outcome was assessed), as was described in a systematic review of two trials.[6] It could be argued that joint injections are used for their rapid, short-term effects before or contemporaneously with physical therapy because benefits with injections in the short term (6 weeks) have been shown to be greater than those with placebo.[7] However, there was no evidence in the current trial to suggest that injections were more beneficial than physical therapy at 4 or 8 weeks. Another controlled trial also showed that a glucocorticoid injection administered 2 weeks before a course of exercise therapy provided no benefit with respect to reducing pain.[8] If the population in the current trial had been restricted to patients with severe pain, the benefits with injection may have been greater, as was shown in a meta-analysis of individual patient data.[9] Third, the physical therapy program was individualized and included therapist-applied manual techniques combined with home exercises, all of which were based on the clinical judgement of the therapists. Although therapists were provided with guidelines regarding manual therapy and exercise, we do not know how these guidelines were applied; therefore, replication of the findings in the trial may be difficult. Although evidence supports exercise for osteoarthritis of the knee,[10] a systematic review has indicated that the few published trials of manual therapy have generally been of low quality and inconclusive,[1] which probably accounts for the aforementioned recommendations of some medical and research societies against manual therapy for osteoarthritis of the knee. Fourth, a broad assessment of health care costs associated with osteoarthritis of the knee showed almost no difference between groups in the current trial, but formal cost-effectiveness analyses would help inform funding decisions, especially given that the number of physical therapy visits may not be practical in many health care systems. There were fewer knee replacements in the physical therapy group than in the glucocorticoid injection group, although the total number was small — a finding that warrants further investigation. Finally, because the trial was conducted in a U.S. military population, the generalizability of the conclusions may be limited.

This relatively small trial, conducted predominantly in one center, provides evidence to support a greater benefit with physical therapy involving manual therapy and exercise than with glucocorticoid injection. The results do not exclude a role for joint injection for treatment of a flare of acute pain, as acknowledged in guideline recommendations,[1,2] but the implication could be that injections should not be used first, nor should they be used in place of a physical therapy program that includes exercise to manage symptoms of osteoarthritis of the knee. Challenges remain as to how to change the referral behavior and treatment decisions of clinicians and how to provide health service models that offer nondrug and nonsurgical approaches in the treatment of patients with osteoarthritis of the knee.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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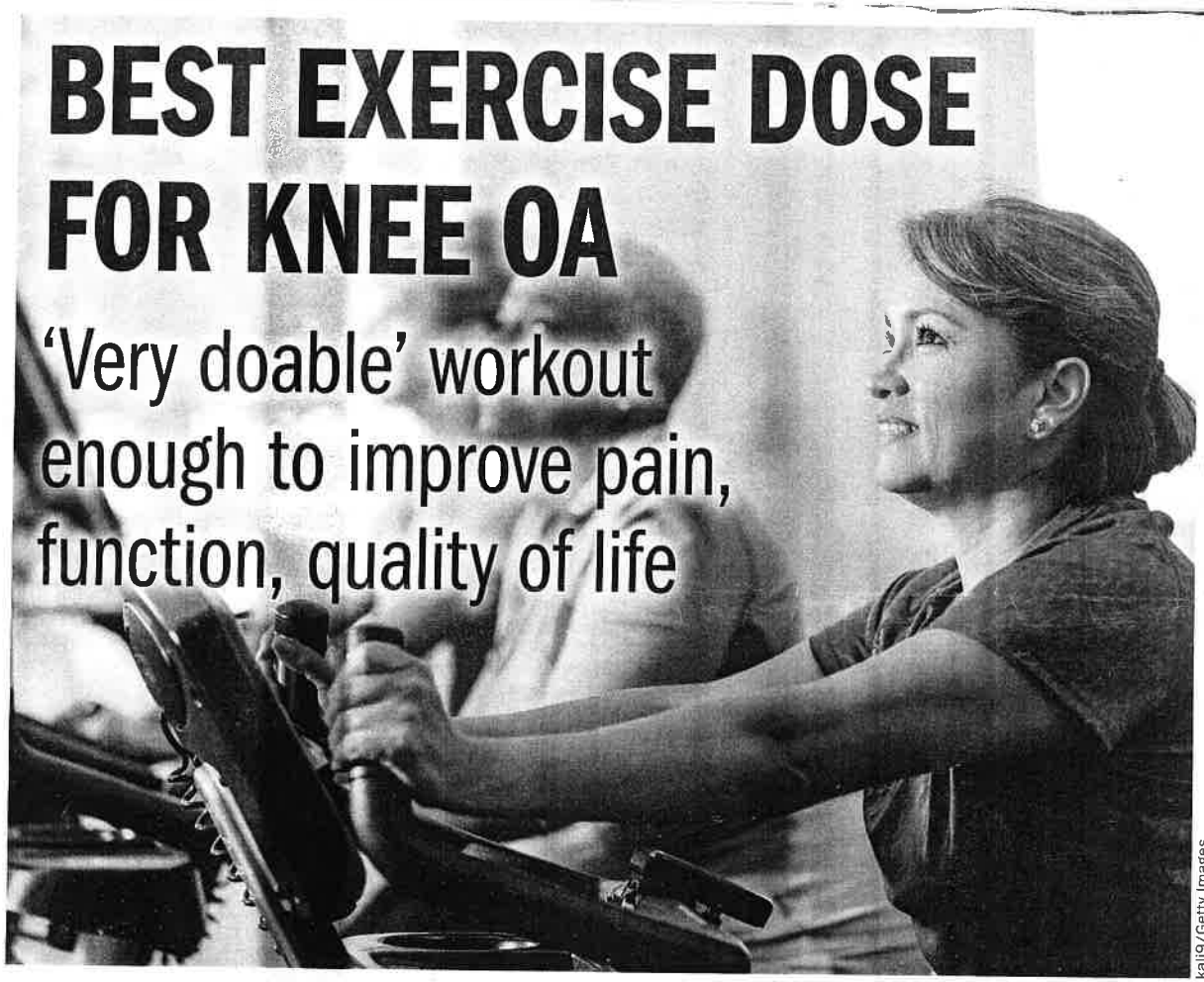
BEST EXERCISE DOSE FOR KNEE OA

'Very doable' workout enough to improve pain, function, quality of life



kali9/Getty Images

BY JAKE REMALY
FROM ANNALS OF INTERNAL MEDICINE

Exercise helps patients with knee osteoarthritis, but more isn't necessarily better, new research shows.

A low-dose exercise regimen helped patients with knee OA about as much as a more intense workout plan, according to trial results published online in Annals of Internal Medicine (2023 Jan 23. doi: 10.7326/M22-2348).

Both high and low doses of exercise reduced pain and improved function and quality of life.

The improvements with the lower-dose plan and its 98% adherence rate are encouraging, said Nick Trasolini, MD, assistant professor of orthopedic surgery at Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, N.C.

"This is a very doable amount of medical exercise therapy for patients with knee osteoarthritis, and one that makes a big difference in patient-reported symptoms," Dr. Trasolini, who was not involved in the study, said in an interview.

See **KNEE OA** on page **2** ▸

Commentary

75 years of methotrexate

A look back on the fascinating history of folate antagonists

BY DAVID M. WARMFLASH, MD

If you could go back in time 75 years and tell Dr. Sidney Farber, the developer of methotrexate for cancer therapy, that 21st-century medicine would utilize his specially designed drug more in rheumatology than oncology, he might be surprised. He might scratch his head even more, hearing of his drug sparking interest in still other medical fields, such as cardiology.

But drug repurposing is not so uncommon. One classic example is aspirin. Once the most common pain medication and used also in rheumatology, aspirin now finds a range of applications, from colorectal cancer to the prevention of cardiovascular and cerebrovascular thrombosis. Minoxidil is another example, developed for hypertension but used today mostly to stop hair loss. Perhaps most ironic is thalidomide, utilized today for leprosy and multiple myeloma, yet actually contraindicated for its original application, nausea of pregnancy.

Methotrexate, thus, has much in common with other medical treatments, and yet its origin story is as unique and as fascinating as the story of Dr. Farber himself. While this is a rheumatology article, it's also a story about the origin of a particular rheumatologic treatment, and so the story of that origin will take us mostly through a discussion of hematologic malignancy and of the clinical

See **METHOTREXATE** on page **16** ▸

KNEE OA Fewer exercises, less time still beneficial

continued from page 1

What's the right dose?

Exercise is a go-to treatment for knee OA, but the precise dose to recommend has been unclear. To study this question, Tom Arild Torstensen, MSc, RPT, with Karolinska Institutet, Huddinge, Sweden, and Holten Institute, Stockholm, and colleagues conducted a trial at four centers in Sweden and Norway.

The study included 189 men and women with knee OA. Participants were randomly assigned to low- or high-dose exercise plans, which they performed three times per week for 12 weeks under the supervision of a physiotherapist.

Participants in the high-dose group performed 11 exercises during each session, which lasted 70-90 minutes.

The low-dose regimen consisted of five exercises – cycling, squats, step-ups, step-downs, and knee extensions – performed for 20-30 minutes.

The researchers measured outcomes using the Knee Injury and Osteoarthritis Outcome Score, which assesses pain, other symptoms, function in daily living, function in sports and recreation, and knee-related quality of life.

"Patients in both groups improved significantly over time, but high-dose exercise was not superior to low-dose exercise in most comparisons," the study investigators reported.

High-dose exercise was associated with better function in sports and recreational activity and knee-related quality of life at 6 months. Those differences did not persist at 1 year, however. The researchers reported no safety concerns with either intervention.

Adherence was "nearly perfect" in the low-dose group. It was slightly lower in the high-dose group, the researchers said.

"Interestingly, it seems that high-dose treatment could be preferable to low-dose treatment in the long run for people who lead active lives," they wrote. "This should be the subject of future studies."

All clinical practice guidelines for knee OA recommend exercise, but "we do not know the optimal dose," Kim Bennell, PhD, a research physiotherapist at the University of Melbourne, said in an interview.

Dose has components, including number of times per week, number of exercises, sets and repetitions, intensity, and duration of exercise sessions, Dr. Bennell said.

"These results suggest that an exercise program that involves less time and fewer exercises can still offer benefits and may be easier for patients to undertake and stick at than one that involves greater time and effort," she said.

The study was supported by the Swedish Rheumatic Fund. Dr. Trasolini and Dr. Bennell have disclosed no relevant financial relationships.

Review: Running does not cause lasting cartilage damage

BY BIANCA NOGRADY
FROM OSTEOARTHRITIS AND CARTILAGE

Running does not appear to cause sustained wear and tear of healthy knee cartilage, with research suggesting that the small, short-term changes to cartilage after a run reverse within hours.

A systematic review and meta-analysis published in Osteoarthritis and Cartilage (2022 Nov 16. doi: 10.1016/j.joca.2022.09.013) presents the findings involving 396 adults, which compared the "before" and "after" state of healthy knee cartilage in runners.

Running is often thought to be detrimental to joint health, wrote Sally Coburn, PhD candidate at the La Trobe Sport & Exercise Medicine Research Centre at La Trobe University in Melbourne and coauthors, but this perception is not supported by evidence.

For the analysis, the researchers included studies that looked at either knee or hip cartilage using MRI to assess its size, shape, structure, and/or composition both in the 48 hours before a single bout of running and in the 48 hours after. The analysis aimed to include adults with or at risk of osteoarthritis, but only 57 of the 446 knees in the analysis fit these criteria.

In studies where participants underwent MRI within 20 minutes of running, there was an immediate postrun decrease in the volume of cartilage, ranging from –3.3% for weight-bearing femoral cartilage to –4.1% for tibial cartilage volume. This also revealed a decrease in T1 and T2 relaxation times, which are specialized MRI measures that reflect the composition of cartilage and which can indicate a breakdown of cartilage structure in the case of diseases such as arthritis.

Reversal of short-term cartilage changes

However, within 48 hours of the run, data from studies that repeated the MRIs more than once after the initial prerun scan suggested these changes reversed back to prerun levels.

"We were able to pool delayed T2 relaxation time measures from studies that repeated scans of the same participants 60 minutes and 91 minutes post-run and found no effect of running on tibiofemoral joint cartilage composition," the authors write.

For example, one study in marathon runners found no difference in cartilage thickness in the tibiofemoral joint between baseline and at 2-10 hours and 12 hours after the marathon. Another showed the immediate postrun decrease in patellofemoral joint cartilage thickness had reverted back to prerun levels when the scan was repeated 24 hours after the run.

"The changes are very minimal and not inconsistent with what's expected for your cartilage which is functioning normally," Ms. Coburn told this news organization.

pojoslaw/Thinkstock

Sparse data in people with osteoarthritis

The authors said there were not enough data from individuals with osteoarthritis to be able to pool and quantify their cartilage changes. However, one study in the analysis found that cartilage lesions in people considered at risk of osteoarthritis because of prior anterior cruciate ligament reconstruction were unchanged after running.

Another suggested that the decrease in femoral cartilage volume recorded at 15 minutes persisted at 45 minutes, while a separate study found significantly increased T2 relaxation times at 45 minutes after a run in those with knee osteoarthritis but not in those without osteoarthritis.

Ms. Coburn

> "The **changes [postrun] are very minimal and not inconsistent with what's expected** for your cartilage which is functioning normally."

> "We really **don't know yet if running is safe for people with osteoarthritis.** We need much more work in that space."

Dr. Culvenor

Senior author Adam Culvenor, PhD, senior research fellow at the La Trobe Centre, said their analysis suggested running was healthy, with small changes in cartilage that resolve quickly, but "we really don't know yet if running is safe for people with osteoarthritis," he said. "We need much more work in that space."

Overall, the study evidence was rated as being of low certainty, which Dr. Coburn said was related to the small numbers in each study, which in turn relates to the cost and logistical challenges of the specialized MRI scan used.

"Study of a repeated exposure over a long duration of time on a disease that has a long natural history, like osteoarthritis, is challenging in that most funding agencies will not fund studies longer than 5 years," Grace Hsiao-Wei Lo, MD, of the department of immunology, allergy, and rheumatology at the Baylor College of Medicine in Houston, said in an email.

Dr. Lo, who was not involved with this review and meta-analysis, said there are still concerns about the effect of running on knee osteoarthritis among those with the disease, although there are some data to suggest that among those who self-select to run, there are no negative outcomes for the knee.

An accompanying editorial (Osteoarthritis Cartilage. 2023 Feb. doi: 10.1016/j.joca.2022.11.002) noted that research into the effect of running on those with osteoarthritis was still in its infancy. "This would help to guide clinical practice on how to support people with osteoarthritis, with regard to accessing the health benefits of running participation," write Jean-Francois Esculier, PhD, PT, from the University of British Columbia, Vancouver, and Christian Barton, PhD, with the La Trobe Centre, pointing out there were a lack of evidence-based clinical recommendations for people with osteoarthritis who want to start or continue running.

It's a question that PhD candidate Michaela Khan, MSc, is trying to answer at the University of British Columbia. "Our lab did a pilot study for my current study now, and they found that osteoarthritic cartilage took a little bit longer to recover than their healthy counterparts," Ms. Khan said. Her research is suggesting that not only can people with osteoarthritis run, but that even those with severe disease, who might be candidates for knee replacement, can run long distances.

Commenting on the analysis, Ms. Khan said the main take-home message was that healthy cartilage seems to recover after running, and that there is not an ongoing effect of "wear and tear."

"That's changing the narrative that if you keep running, it will wear away your cartilage, it'll hurt your knees," she said. "Now, we have a good synthesis of scientific evidence to prove maybe otherwise."

Ms. Coburn and Dr. Culvenor report grant support from the National Health & Medical Research Council of Australia, and another author reports grant support from the U.S. National Institute of Arthritis and Musculoskeletal and Skin Diseases. The authors, as well as Dr. Lo and Ms. Khan, report no relevant financial relationships.

Inflammation, immunity troubles top long-COVID suspect

BY SOLARINA HO

Nonstop inflammation and immune problems top the list of potential causes of long COVID, but doctors say it's growing clear that more than one thing is to blame for the wide swath of often debilitating symptoms that could last months or even years.

"I think that it's a much more complex picture than just inflammation, or just autoimmunity, or just immune dysregulation. And it's probably a combination of all three causing a cascade of effects that then manifests itself as brain fog, or shortness of breath, or chronic fatigue," says Alexander Truong, MD, a pulmonologist and assistant professor at Emory University, Atlanta, who also runs a long-COVID clinic.

Long COVID, post–COVID-19 condition, and postacute sequelae of SARS-CoV-2 (PASC) are among the terms used by the National Institutes of Health to describe the long-term health issues faced by an estimated 10%-30% of people infected with COVID-19. Symptoms – as many as 200 – can range from inconvenient to crippling, damage multiple organ systems, come and go, and relapse. Long COVID increases the risk of worsening existing health problems and triggering new ones, including cardiovascular disease and type 2 diabetes.

So far, research suggests there is no single cause, condition, or disease that explains why some people have an extensive range of symptoms long after the early COVID-19 infection has cleared up. Many experts believe some combination of biological processes – including the virus hanging around in our bodies, inflammation, autoimmunity, tiny blood clots, immune system problems, and even the reactivation of dormant viruses such as the Epstein-Barr virus – could be the culprit, a theory also supported by a comprehensive and in-depth review of long-COVID studies published in the journal Nature Reviews Microbiology (2023 Jan 13. doi: 10.1038/s41579-022-00846-2).

"It's become clear over the last couple of years that there are different [symptoms] of long COVID ... that cannot all be lumped together," says Michael Peluso, MD, an assistant professor of medicine and an infectious diseases doctor at the University of California, San Francisco.

Inflammation and a virus that hangs around

Multiple studies have shown that the virus or pieces of it can remain in many parts of the body, including the kidneys, brain, heart, and gastrointestinal system, long after the early infection.

"One major question that I think is the area of most intense investigation now is whether there is viral persistence that is driving immune dysregulation and therefore symptoms," says Dr. Peluso.

A small Harvard University study (Clin Infect Dis. 2022 Sep 2. doi: 10.1093/cid/ciac722), for example, found evidence that reservoirs of the coronavirus could linger in patients up to a year after they're first diagnosed.

An earlier German study (Cell Rep Med. 2022 Jun 21. doi: 10.1016/j.xcrm.2022.100663) found that patients with post–COVID-19 symptoms had higher levels of three cytokines – small proteins that tell the body's immune system what to do and are involved in the growth and activity of immune system cells and blood cells. Researchers said the results supported the theory that there is persistent reprogramming of certain immune cells, and that the uncontrolled "self-fueled hyperinflammation" during the early COVID-19 infection can become continued immune cell disruption that drives long-COVID symptoms.

"Long COVID is more likely due to either an inflammatory response by the body or reservoirs of virus that the body is still trying to clear ... and the symptoms we're seeing are a side effect of that," says Rainu Kaushal, MD, senior associate dean for clinical research at Weill Cornell Medicine in New York.

An autoimmune condition?

But inflammation alone does not fully explain post–COVID-19 problems.

Dr. Truong and his team, for example, have been documenting inflammatory markers in patients at the post-COVID clinic he cofounded more than 2 years ago at Emory Executive Park in Atlanta. When the clinic was first launched, high-dose NSAIDs – including ibuprofen – and prednisone were prescribed to long-COVID patients.

"It didn't make a difference at all for any of these folks," he says, adding that there are signs that autoimmunity is at play. But he cautions that it is still too early to suggest treating long-COVID patients with medications used for other autoimmune conditions.

A small study published in Science Translational Medicine (2022 Dec 21. doi: 10.1126/scitranslmed.add0484) found that, among patients who failed to regain their sense of smell long after their initial infection, there was inflammation in the nose tissue where smell nerve cells are found, even though no detectable virus remained. Fewer olfactory sensory neurons were seen, as well – findings that researchers said resembled some kind of "autoimmune-like process."

> "It's not like with COVID, where the path towards a great and meaningful solution to this unbelievable problem was clear – we need a vaccine. **It's going to be a long haul to figure out what is going on.**"

Meanwhile, scientists in Canada found signs of autoimmunity in blood samples taken from patients who still had fatigue and shortness of breath after their initial COVID-19 infection. Two specific proteins were present a year after infection in up to 30% of patients, many of whom still had shortness of breath and fatigue, the researchers reported in the Jan. 1 issue of the European Respiratory Journal (2023. doi: 10.1183/13993003.00970-2022). These patients had been healthy and had no autoimmune condition or other diseases before they were infected.

Immune system problems

A number of studies have suggested that a problematic immune response could also explain why symptoms persist for some people.

Researchers in France (J Med Virol. 2022 Oct 13. doi: 10.1002/jmv.28209), for example, found that the immune response problems in those with severe COVID-19 infections caused exaggerated or uncontrolled formation of a type of bug-fighting defense mechanism called a neutrophil extracellular trap, which in turn triggers harmful inflammation that can result in multiorgan damage. These traps are netlike structures made from fibers composed mostly of DNA strings that bind, or trap, pathogens.

Long COVID is not like an acute infectious disease, says Alexander Charney, MD, PhD, the lead principal investigator of the RECOVER adult cohort at Mount Sinai in New York, and an associate professor at Icahn School of Medicine at Mount

is more similar to other comp
chronic diseases that have tak
cades to understand, such as h
disease, mental illness, and rh
tologic diseases, he says.

Biomarkers and blood clot

Scientists are homing in on bi
ers, or detectable and measur
traits – in this case, molecular
tors – that can make diagnosir
COVID easier and give better
tion for treatment. These bion
are also key to helping sort ou
complex biology of long COV

In one study, data from blooc
ples taken from hundreds of h
talized COVID-19 patients sug
changes are happening at the n
lar level during initial severe inf
These changes may be tied to t
velopment of longer-term sym
according to the study by Dr. C
and his team at Mount Sinai pu
in Nature Medicine (2022 Dec 8
10.1038/s41591-022-02107-4).

Blood clotting issues have als
detected in long-COVID patien
least one study (J Med Virol, 20
13. doi: 10.1002/jmv.28209) fou
signs that long-COVID patients
higher levels of a type of auto-a
body linked to the abnormal fo
tion of clots. Researchers suspe
tiny, persistent microclots – und
able via regular pathology tests
be cutting off oxygen flow to tis
by blocking capillaries – and co
plain many of the post-COVID
toms described by patients.

While enormous progress has
made toward understanding lon
COVID, the research is still consi
early and faces many challenges,
cluding varying criteria used to d
the condition, the types and qual
data used, differences in how pati
are defined and recruited, and th
size of many studies. Some resea
also appears to conflict with othe
studies. And while there are speci
ized tools for diagnosing some as
of the condition, standard tests o
don't detect many of the signs se
long-COVID patients. But given t
gency and global scale of the prol
experts say more funding and sup
should be prioritized.

"People are suffering now, and
want answers now. ... It's not lik
with COVID, where the path to
a great and meaningful solution
this unbelievable problem was c
we need a vaccine," says Dr. Ch

"It's going to be a long haul to
ure out what is going on."

FROM CONSUMER REPORTS

The facts about collagen supplements

BY SALLY WADYKA

ISTOCK

Collagen is the most abundant protein in our bodies. It's used to make all our connective tissues — including skin, bones, blood vessels, cartilage, ligaments, muscles and tendons. That has led scientists to look into whether consuming collagen supplements can keep skin and joints youthful as we age. The answer is maybe.

Meanwhile, collagen supplements are already popular. In a recent Consumer Reports' nationally representative survey of more than 3,000 U.S. adults, 7 percent of men and 19 percent of women said they've used collagen. And among the 27 percent of Americans who said they've ever taken any type of supplements for nail, skin or hair health, 3 in 10 have used collagen for that reason.

Here's what you need to know if you're considering taking a collagen supplement.

What does it do?

"Collagen is like the frame of your mattress, providing necessary structure and support to tissues in the skin and other areas of the body," says Joshua Zeichner, associate professor of dermatology at Mount Sinai Hospital in New York.

When you're young, the body continually produces new collagen and degrades the old — meaning there's always a plentiful supply to feed those connective tissues. But as with many things, production of it slows down as we age. Lifestyle factors can also affect your supply.

"Sun exposure, smoking, excessive alcohol or sugar intake, lack of sleep and being sedentary can accelerate the loss of collagen," says Jamie I. Baum, director of the Center for Human Nutrition at the University of Arkansas in Fayetteville. Before you know it, you're losing collagen faster than you can replace it.

Without the structure that collagen fibers provide, skin starts to sag and wrinkle. Without enough fresh, spongy collagen in your cartilage, tendons, ligaments and joints can be less flexible.

What about the science?

The research is far from definitive, but "some data suggests that collagen supplementation does have a beneficial effect on collagen turnover rates in older adults," says Keith Baar, professor of molecular exercise physiology at the University of California at Davis.

A 2017 review of several small studies of people with osteoarthritis concluded that daily collagen supplements (between 10 milligrams and 40 mg) decreased reported joint pain by 26 to 33 percent. And a 2018 study, published in the journal Nutrients, looked at the effect of collagen on bone density in postmenopausal women. Those who took a 5-gram collagen supplement had significant increases in the spine and neck vs. those who got a placebo. (The study was partly funded by a supplement manufacturer.)

"I do think that future research will show more positive effects," Baar says. "But the quality of the current data isn't super-high, and we need evidence from large, long-term trials."

And supplements have a downside: They aren't regulated by the Food and Drug Administration, so there's no guarantee that you're getting exactly what the package claims.

Heavy metal contamination is also a concern. In 2020, the Organic Consumers Association and the Clean Label Project tested 28 brands of collagen supplements and found that many contained arsenic, lead, mercury and cadmium.

Best ways to get this protein

For now, you can enhance collagen production by following a healthy diet.

Collagen is found naturally in animal protein, such as meat and fish.

"Bone broth and tough cuts of meat, like brisket or pot roast, contain lots of connective tissue, which is made up of collagen," Baum says. But you don't need to eat collagen to make collagen. "When you eat any type of protein [animal- or plant-based], your body breaks it down into individual amino acids," Baum says. These are reassembled to make proteins your body needs, including collagen.

"The type of protein doesn't matter as much as making sure you're getting adequate amounts of essential amino acids in your diet," she says. For older adults, that's about 25 to 30 grams of protein per meal.

We know that vitamin C, zinc and copper help with collagen production, and other dietary factors may also play a role. Researchers in Baar's lab are looking at micronutrients (such as phytoestrogens in soy and polyphenols in dark chocolate) that may increase the body's ability to make more collagen even as we age.

"I have a feeling we're going to find that groups who traditionally eat those foods will show lower rates of musculoskeletal problems," he says.

Metabolic arthropathies: disorders of joint function caused by metabolic imbalances which target the joints that otherwise are innocent bystanders

A. GOUT :

1. chemistry of pathogenesis

a. mishandling of purine metabolism, byproduct of protein metabolism

b . overproduction , underexcretion
lost in evolutionary development.

2. physical pathogenesis: hyperuricemia – high blood levels leading to concentration and precipitation in and around joints (lower temperature affects solubility), kidneys (changes in pH – acid balance) reduces solubility

3. gouty arthritis: a severe, painful condition occurring in joints due to presence of uric acid crystals and the inflammatory response they cause

a. crystals are composed of monosodium urate – which may be present in asymptomatic joints

b. white blood cells (PMNs) react to presence of these crystals by releasing enzymes which activate an intense inflammatory response - classic arthritis

c. attacks will resolve after 3 to seven days and may not recur for years (the intercritical period)

1. invariably will return – damage to joints results from summation of each individual episode so that in time a characteristic picture of secondary osteoarthritis can be seen physically and radiographically

2. joints of predilection – feet - first MTP, ankles Achilles tendon and bursa of the heel, knees , elbows - olecranon bursae – chronic tophaceous gout

4. Kidney stones (nephrolithiasis): concretions of uric acid that form from hyperconcentration in the collecting system and are passed into the ureter (the conduit that transfers urine from the kidney to the urinary bladder

5. cardiovascular disease : effect of proinflammatory risk

B. Pseudogout (calcium pyrophosphate deposition disease - CPPD): arthritic condition resulting from disorders in normal metabolism causing deposition of crystalline material in characteristic fibrocartilage locations

1. associated conditions

a. hemochromatosis : disorder of iron metabolism resulting of increase in total body iron stores

b. hyperparathyroidism : disorder of overactivity of parathyroid glands causing increased production of parathyroid hormone and increase in calcium production

c. acromegaly – overproduction of growth hormone

d. Wilson's disease – disorder of copper metabolism

e. electrolyte deficiency – phosphorous, magnesium

2. diagnostic considerations :

a. joint (synovial) fluid analysis

b. radiography

c. blood/ serum for detection of metabolic , endocrinologic imbalances mentioned above

C. Hydroxyappetite

D. Oxalate

E. Corticosteroid (post injection)