Managing the Pain of Knee Osteoarthritis

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Abstract: Pain from knee osteoarthritis creates a significant burden for symptomatic patients, who are often forced to change their lifestyle because of their symptoms. Activity modification, therapy, weight loss, nonsteroidal anti-inflammatory drugs, shoe orthotics, bracing, and injections are the nonoperative options available. New technologies are also emerging in the treatment of knee osteoarthritis. Ultimately, these therapeutic modalities should reduce pain and increase the overall functioning of patients. These nonoperative modalities give the clinician several effective options before surgical management is considered.

Keywords: knee; osteoarthritis; pain; treatment

Introduction

Osteoarthritis (OA) is increasingly common with advancing age, but patients want to maintain an active lifestyle. Consequently, they seek treatment. With a higher level of physical activity, there is a greater chance that prior articular cartilage damage will develop into symptomatic OA. Osteoarthritis affects up to 27 million people in the United States and can create up to $15 billion in estimated economic burden.[1,2] It has been estimated that OA causes disabling knee symptoms in 10% of people aged > 55 years.[3] Many of these patients can be severely disabled.

Osteoarthritis is often referred to as *degenerative joint disease* or simply as *degenerative arthritis,* a term that reflects the progression of mechanical problems and associated symptoms arising from the degeneration of the knee joint's articular cartilage and the subsequent effect on the subchondral bone. There are 2 types of OA: primary, which develops from an unknown cause, and secondary, for which a specific cause can be determined. Causes of secondary OA include trauma (such as the effects of meniscectomy), rheumatologic conditions, congenital deformities, and sometimes endocrine or metabolic abnormalities.

Patients with knee OA present with multiple symptoms related to joint degeneration and inflammation. These include pain, swelling, stiffness, crepitus, mechanical symptoms (catching and locking), and loss of motion. All of these symptoms affect the patient's lifestyle and mobility. With OA, the articular/hyaline cartilage damage in the synovial joint eventually leads to bony changes. Advanced disease is visible on plain radiographs and includes narrowing of the joint space, osteophytes, and subchondral cysts (Figure 1).

Risk factors for developing OA include advanced age, female sex, prior joint injury, a positive family history, and obesity. Although an elevated body mass index increases the probability of knee OA progression, its effect is further increased in knees with malalignment.[4] Meniscus tearing is associated with OA (Figure 2). With progression of the OA, the meniscal damage can be associated with complete articular cartilage loss of

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1 or both joint surfaces (Figure 3). A recent report demonstrated that knees with radial meniscus tears and meniscal extrusion were at greater risk for the later development of OA.[5] Sex differences also exist, as women generally present for treatment later than men and with their OA more advanced. They tend to have more debilitating pain than their male counterparts.[6]

Aging is a risk factor for the development of knee OA, in part because the ability of articular cartilage to heal decreases as a person ages. Also, the older the individual, the greater the cumulative trauma he or she has experienced. This is not to say that young individuals cannot develop OA, but those who do usually have sustained significant trauma leading to this development. Other risk factors for knee OA include infection,[7,8] obesity,[9] repeated stresses from athletic competition,[10] and workplace trauma.[11,12]

Reflecting the growing incidence of OA, the frequency of knee surgery for OA in patients aged < 55 years has doubled during the last 10 years.[13] But there are several nonoperative approaches that can reduce the symptoms of OA,[14] such as activity modification, weight loss, and nonsteroidal anti-inflammatory drug. Physical therapy,[15,16] shoe inserts,[17,18] knee bracing,[19,20] and knee injections[21,22] are other therapeutic options that may reduce the symptoms of OA. The main goal of all these therapeutic modalities is to reduce pain and increase the overall functioning of the patient.

Treatment Options

Activity Modification and Physical Therapy

The pain of knee OA leads to muscle weakness, altered muscle function, reduced proprioception and postural control, joint instability, restricted range of motion, and lower aerobic fitness.[23] An initial supervised physical therapy program is often underutilized. Such a physical therapy program should be designed to lead to increased and appropriate activity.

Figure 1. Advanced disease is visible on plain radiographs and includes narrowing of the joint space, osteophytes, and subchondral cysts.

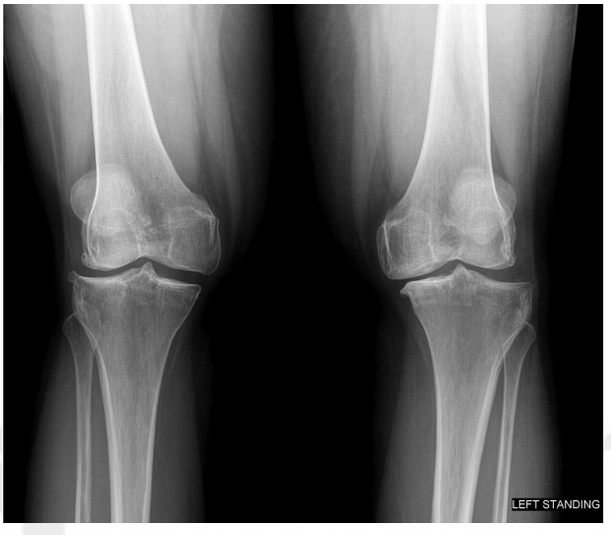
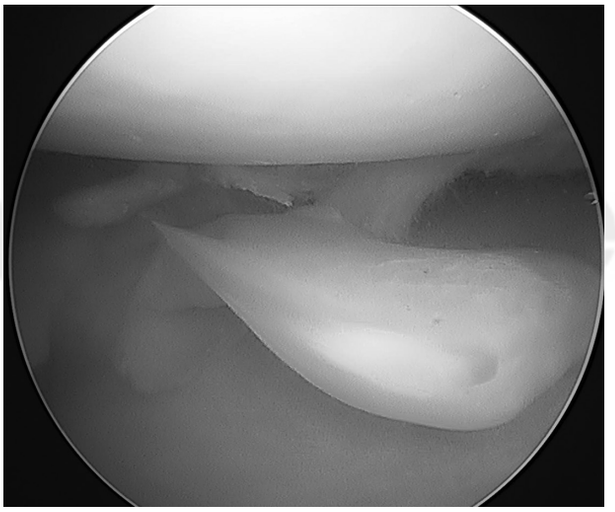


Figure 2. Meniscus tearing can cause significant joint symptoms, which are eliminated by removal.

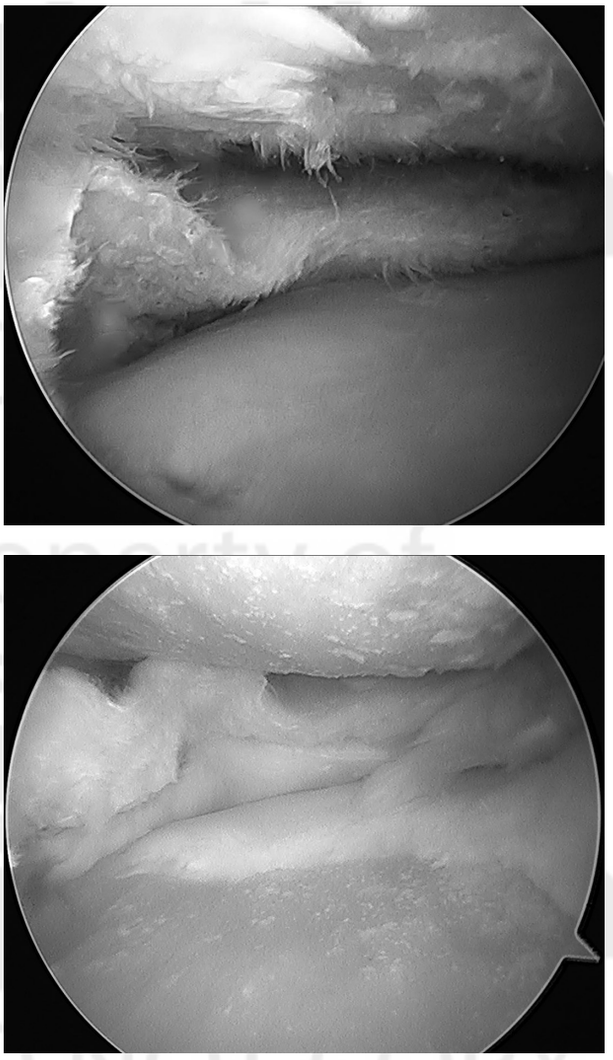


Exercise programs can be beneficial. They may focus on aerobic (isotonic) or resistance (isometric) exercise. With more advanced OA, the emphasis changes to increasing joint flexibility and range of motion. If available, an aquatic program, which enables strengthening in an unloaded environment, can be extremely effective. However, recent evidence suggests that land-based exercise programs can provide short-term reductions in knee pain and improved knee function.[16] The approach selected should be tailored to the patient's physical condition, the resources available, and the patient's preferences.

Adults with OA are more likely to be physically inactive than are those without OA. In a review of 13 randomized controlled trials, both aerobic walking and home-based quadriceps strengthening exercises reduced the pain and disability from knee OA. Additionally, no differences were found between these exercises on indirect comparison[24]; neither exercise was superior to the other. The most important factor in receiving benefits from an exercise program is continuing participation in the program. Although the best way to deliver strengthening exercise is unclear, it is important to encourage patients with knee OA to continue the exercise program beyond the initial supervised period.

Although therapy cannot mechanically alter the loads going through the knee or alter the disease process of knee OA, the exercises associated with therapy can help alter some of the symptoms and decrease pain. Water therapy has

Figure 3. With progression of the osteoarthritis, the meniscal damage is associated with complete articular cartilage loss, which can be limited to 1 joint surface (**A**) or involve both the femur and tibia (**B**).



been shown to be productive in older patients with lower limb arthritis.[16]

Weight Loss

Decreasing the load on a painful joint reduces symptoms. This can be accomplished by both activity modification and weight loss, which reduce the loads on the knee and thus decrease pain and swelling, which in turn improves the patient's ability to participate in physical activity and slows the progressive deterioration of the knee articular cartilage. A randomized controlled study demonstrated that weight loss led to significant improvement in knee pain, stiffness, and function.[25] As little as a 10% reduction in body weight can result in a marked decrease in knee joint compressive loads during walking as compared with patients with little or no weight loss.[26]

Greater weight loss results in even more significant improvement. However, weight loss in the elderly should be approached with caution because it can be associated with the loss of muscle and bone mass, which can result in the increased risk of falling and fractures. Thus, a very cautious approach should be taken in recommending weight loss for the elderly, and generally it should be limited to those with a body mass index > 30 kg/m^2.[9]

Pharmacologic Therapy

Acetaminophen

Acetaminophen is a safe and effective treatment for patients with mild-to-moderate knee OA and is often recommended as the initial pharmacologic treatment for knee OA. Although it offers no anti-inflammatory activity, it is generally viewed as the safest analgesic medication on the gastric mucosa, blood pressure, and renal function, and it can provide oral analgesia for knee OA over the long term. However, recent concerns about its renal and hepatic toxicity must be considered when determining dosing levels. That being said, acetaminophen still has less toxicity than other analgesic medications and should be considered for the initial treatment of knee OA.

Nonsteroidal Anti-inflammatory Drugs

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are common treatment modalities prescribed for patients with early OA. They are designed to reduce the inflammatory markers associated with knee OA and may be more effective than acetaminophen in pain control. A systematic review of the use of NSAIDs for knee OA failed to show any difference in the types or dosages of NSAIDs,[27] and so the authors of the review recommended that the selection of NSAIDs be physician dependent and based on safety and cost.

Although these medications are possibly the most accessible for patients, they entail significant associated risks. Gastrointestinal effects are a fairly common symptom, which can be reduced by using a cyclooxygenase-2 inhibitor. Patients with cardiovascular or renal impairment may want to avoid NSAID use. Additionally, NSAIDs should be prescribed cautiously in elderly patients because of their effects on the kidneys, blood pressure (more so with COX-2 inhibitors), cardiovascular system, and the gastrointestinal tract.

Recent evidence indicates that some sustained release medications are effective. Controlled-release tramadol has been shown to be as effective as sustained-release diclofenac in the treatment of pain due to knee OA, with the potential for fewer serious side effects than with NSAID administration.[28]

In prescribing NSAIDs, the lowest effective dose should be used and in the elderly, and prescribing a proton pump inhibitor along with NSAIDs should be considered.

The topical use of NSAIDs, if effective, would avoid the potential for adverse events and offer a desirable long-term treatment option. However, the absorption rates and the penetration depth with topical applications are variable, and systemic absorption can occur. Topical formulations of ultradeformable phospholipid vesicles containing ketoprofen have been shown to be effective.[29]

Opioids

Opioids are clearly not the first-line medication for knee OA and should not be used if there are any other options. When used in patients who may need surgery, the opiate sensitivity can be adversely affected and make postoperative pain control difficult. However, if the proper guidelines are followed, opioids can be safely used for short-term severe pain even in the elderly. Opioids are sometimes indicated for moderate-to-severe pain when previously prescribed NSAIDs have become ineffective or are contraindicated. A high index of suspicion must be maintained regarding the potential for opioid misuse.

Additionally, patients prescribed opioids should be counseled about the potential for constipation, nausea, and excessive sedation with their use. Tramadol is a centrally acting analgesic with weak opioid activity and has been shown to have an efficacy similar to that of sustained-release diclofenac in patients with knee or hip OA. It has a lower potential for the serious side effects that characterize NSAID administration.[28]

Glucosamine and Chondroitin

The use of glucosamine and chondroitin sulfate has received a great deal of publicity in recent years. Oral glucosamine is a dietary supplement, not a drug. It is commonly sold as glucosamine sulfate, glucosamine hydrochloride, and *N*-acetylglucosamine. Glucosamine is an endogenously synthesized hexosamine involved in the formation of hyaluronic acid, proteoglycans, glycolipids, and glycoproteins, which are important constituents of articular cartilage.

Chondroitin sulfate is a structural part of the extracellular matrix that is essential for pressure resistance through retaining water within the cartilage. Most studies utilize 1500 mg of glucosamine and 1200 mg of chondroitin sulfate daily. When effective, the results are apparent 2 to 3 weeks after starting treatment, and persist for a prolonged period. If no response is noted within 6 months, treatment should be discontinued.

A large multicenter, double-blind, placebo- and celecoxib-controlled trial did not find that glucosamine and chondroitin sulfate alone or in combination were effective in treating patients with knee OA.[30] A total of 1583 patients with symptomatic knee OA were enrolled in the trial. Different groups of patients were given 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, both glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or a placebo for 24 weeks. Overall, glucosamine and chondroitin sulfate were not significantly better than placebo in reducing knee pain by 20% in the summed score for the Western Ontario and McMaster Universities Arthritis (WOMAC) pain subscale from baseline. These results are in contrast to a European-based study that reported more optimistic results.[31] That study showed that supplements outperformed (in terms of the primary outcome—pain relief) placebo and Celebrex in the moderate-to-severe arthritis group. However, an insufficient number of patients were enrolled in the moderate-to-severe group to achieve statistical significance. Also, supplements did show reduction in inflammation and improvement in global assessment of response to therapy and assessment of disease status.

Avocado Soy Unsaponifiables

Avocado soy unsaponifiables (ASU) is a preparation of one-third avocado oil and two-thirds soybean oil. It has been extensively studied in Europe and is commonly used as a treatment for OA. A recent study suggests that ASU inhibits the breakdown of cartilage and promotes repair.[32] It may have a chondroprotective effect from an anti-inflammatory and pro-anabolic effect on articular cartilage cells. An active component in ASU has yet to be identified, and variations in commercial preparations may yield different results. The effect of ASU on collagen synthesis may be dose dependent, with greater stimulation at the higher dose levels.

Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids are found in fish, walnuts, and flaxseed, and are known for their anti-inflammatory actions and effect on increasing collagen synthesis. In 2011, a study performed in a guinea pig model assessed the net effect of omega-3 polyunsaturated fatty acids on OA. High omega-3 polyunsaturated fatty acid diets reduced disease in the OA prone guinea pig strain, and most disease markers were modified toward those of the non-OA strain, though not

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all achieved statistical significance. Omega-3 did not increase markers of pathology in either strain.[33]

Injections

Viscosupplementation

Hyaluronic acid (HA) is a glycosaminoglycan—a natural component of cartilage extracellular matrix widely found throughout the body that may contribute to cell proliferation. When HA is injected intra-articularly, it increases synovial fluid viscosity and elasticity, which is called viscosupplementation.

Viscosupplementation is theorized to increase lubrication to the joint, thereby decreasing friction and the symptoms from rough surfaces moving on each other. It is thought clinically that HA can decrease pain and improve physical activity. Although the American Academy of Orthopaedic Surgeons (AAOS) recently changed its clinical practice guidelines to no longer recommend using HA for patients with symptomatic OA of the knee,[14,34] there are multiple studies that show that HA injections help with relief of the symptoms of OA.[35] These changes to the AAOS guidelines resulted from a change in the new minimum clinically important improvement (MCII) criterion. Unfortunately, the AAOS's methodology contains flaws. Research using MCII should only be used as a supplementary instrument rather than the primary basis for clinical decision making. The editors of the *Arthroscopy Journal* point to "evidence-based reports in the same 2013 AAOS CPG [clinical practice guidelines] that some published literature does show clear and statistically significant improvement of knee OA symptoms after viscosupplementation treatment."[36] The bottom line is that "the use of knee hyaluronate viscosupplementation may be clinically insignificant for some patients, but it can be of significant benefit for others."[36]

Although a review and meta-analysis of randomized controlled trials of HA for the treatment of OA showed early short-term pain relief, it did not find increased function.[22] In contrast, a more recent systematic review of 5 published meta-analyses indicates that when the strictest quality tools and interpretation of heterogeneity are used, level I evidence demonstrates that the use of HA in patients with OA results in modest improvement in validated outcomes.[21]

Intra-Articular Corticosteroids

Corticosteroid injections are a commonly used method to reduce the local inflammation due to arthritis. But they only provide short-term relief. Recent systematic reviews failed to identify consistent predictors of a positive clinical response to steroid injections, including radiographic grade, clinical or sonographic evidence of inflammation, or synovial hypertrophy.[37,38] Intra-articular steroids have a rapid onset of action and relatively short-term effectiveness (3–4 weeks). This short-term symptomatic relief appears to be the only evidence-based benefit of a corticosteroid injection into an osteoarthritic knee. Accurate intra-articular placement is not achieved in as many as 45% of these injections,[39–42] and this accuracy varies with the anatomical approach. Serious infections may complicate a knee joint injection and occur as often as 1 in 3000.

The effect of corticosteroid injections are in contrast to HA injections, which have a delayed onset of action and a more prolonged effect. Intra-articular steroid injections showed better pain relief with no functional improvement according to most studies in the literature. However, a consensus about the optimal corticosteroid or the optimal dose has not been established. A systematic review of 21 studies has not identified reliable predictors of response to intra-articular corticosteroid injections.[37] This may not be possible to determine because of the different predictors studied, variable outcome measures, different criteria for symptom change, and missing data. These reviewers concluded that although the data was not consistent across the studies, the likelihood of a positive response to an intra-articular corticosteroid injection may be improved by the following factors: an effusion, knee fluid aspiration, lower disease severity, absence of synovitis, injection delivery under ultrasound guidance, and more severe symptoms at baseline.[38]

Bracing/Orthosis

Osteoarthritis can involve the entire joint or affect a single side (unicompartmental). Unicompartmental involvement, especially medial compartmental arthritis, can be treated with knee bracing or shoe orthotics to address the mechanical alignment (Figure 4). Unloading knee braces can reduce pain, increase function, and reduce excessive loading of the damaged knee compartment. This pain reduction may come from the reduction in muscle co-contractions rather than from medial compartment unloading.[43] Although there are few high-level studies on knee OA bracing, the existing evidence suggests that valgus unloading knee braces for medial compartment knee OA significantly reduce knee adduction angle measures and improve measures relating to medial knee joint loading, as well as gait symmetry and speed. Benefits were demonstrated during walking and during more demanding functional measures, such as running and negotiating stairs.[20] However, there are concerns about

how compliant patients will be in wearing these braces over time.[19]

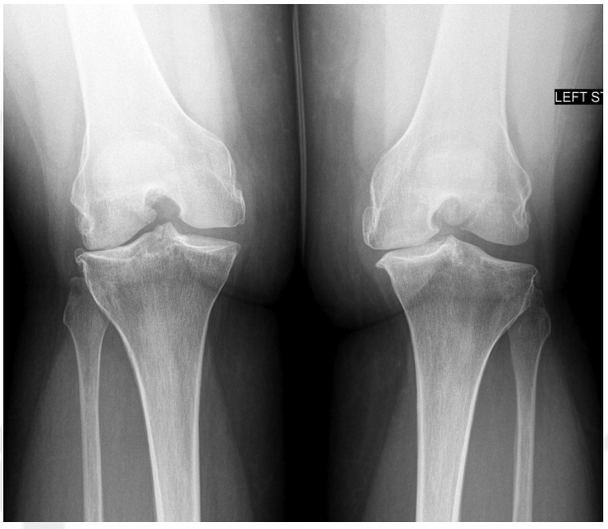
A systematic review found that both short- and mid-term studies indicate that valgus unloading knee bracing decreases pain and disability in medial knee OA more effectively than knee sleeves.[44] In addition, these valgus braces improve the quality of life, knee proprioception, quadriceps strength, and gait symmetry, and decrease compressive loads in the medial knee compartment. Nonetheless, the results of valgus unloading knee bracing are inconsistent.[44] The evidence related to simple knee sleeves suggests that although they may decrease knee pain in OA, they cannot be considered effective treatment for the other aspects of disability related to knee OA.[44] Additionally, the subjective improvement associated with their use is not related to a local thermal effect.

Although biomechanically the angular changes produced with a valgus knee brace are relatively minimal, these braces do result in load sharing and reduce the stresses in the degenerated medial compartment of the knee.[45]

Another mechanical approach to addressing medial compartment OA is a lateral wedge shoe orthotic. Some data support the use of lateral wedge insoles as biomechanically effective and capable of reducing loading of the medial compartment in patients with medial knee OA.[18] Larger (7-mm) wedges have been shown to be more effective in improving the quality of life and decreasing knee joint pain than smaller (3-mm) wedges,[46] although some data indicate that no difference exists between 5° lateral wedges and flat insoles.[47]

A study of 30 patients with idiopathic osteonecrosis of the knee treated for ≥ 3 years with either an insole with a lateral wedge or no insole found that, in those using the insole, the necrotic area and ratio decreased, whereas in the group without the insole they increased. The insole proved to be an effective conservative treatment for the early stages of osteonecrosis of the medial femoral condyle.[48] A meta-analysis of 12 studies found a statistically significant association between the use of lateral wedges and lower pain in medial knee OA.[17]

Figure 4. Knee osteoarthritis involving both knees. The left knee has arthritic changes in the medial compartment, whereas the right knee has collapse and increased angular change in the lateral compartment.



New Concepts

New concepts include injections of platelet-rich plasma (PRP) and bone marrow aspirates; however, prospective randomized controlled trials are required before definitive conclusions can be drawn. The intra-articular injection of mesenchymal stem cells harvested and derived from the inner side of the infrapatellar fat pad was shown to be effective for reducing pain and improving knee function in a series of 18 patients being treated for knee OA.[49] However, this is level IV evidence, and no control group was included in this investigation. Clinical outcomes were measured using subjective scores, and the minimum follow-up was 24 months.

There are currently several abstracts and early published reports showing that PRP injections provide good relief in patients having early arthritis. Several studies have shown more improvement than with HA injections.

Intra-articular PRP injections and viscosupplementation (HA) were compared in 150 patients with early to severe OA. In this prospective comparative level II study, 3 autologous PRP injections provided better and longer efficacy than HA injections in reducing pain and symptoms and in recovering articular function.[35] Another study, a multicenter, double-blind clinical trial, compared the efficacy of an autologous biological therapy (PRGF-Endoret, BTI Biotechnology Institute, Vitoria-Gasteiz, Spain) with HA for the treatment of osteoarthritic knee pain. In this level I study the growth factor–rich plasma showed better short-term results than the HA in relieving mild to moderate OA symptoms.[50]

The technology and clinical utility of the use of both PRP and bone marrow aspirate are being evaluated. A preliminary trial reported that the injection of unfractionated whole bone marrow into osteoarthritic joints in combination with hyperosmotic dextrose achieved complete or near-complete symptomatic relief. However, only 7 patients were included in the study, and there was no control group.[51] The lack of definitive evidence supporting the use of this combination, the absence of insurance reimbursement, and the complexity and cost of these techniques may limit their applicability.

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Longer term and higher quality studies are needed before such modalities can be considered for the management in knee OA.

Surgical Management

If nonoperative treatment fails, surgical intervention should be considered.[13,15,25] Feeley et al[15] recently concluded that when properly indicated, arthroscopic debridement, high tibial osteotomy, unicondylar knee arthroplasty, and total knee arthroplasty allow patients (especially younger ones) with knee OA to maintain an active, healthy lifestyle.

Conclusion

The treatment of a patient with knee OA should consider the patient's needs and challenges. As a start, treatment should attempt to control the mechanical loads on the joint through activity modification and weight control combined with a strengthening program. Mechanical options, including unloading knee bracing and shoe orthotics, may have a role in reducing these loads in selected patients. Medication plays a significant role, and includes the use of acetaminophen and NSAIDs. Glucosamine and chondroitin sulfate have not been shown to be significantly better than a placebo in reducing knee pain. Injectable medications include corticosteroids and viscosupplementation, but the physician should be familiar with the data regarding their effectiveness and counsel the patient accordingly.

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Conflict of Interest Statement

Scott A. Hrnack, MD, has no conflict of interest to declare. F. Alan Barber, MD, is an independent contractor, consultant, speaker, patent holder, and receiver of research funding from Depuy Mitek; a consultant, speaker, and receiver of research funding from Conmed Linvatec; and a receiver of research funding from Arthrex and Biomet, Smith and Nephew, Covidien, Cayenne Medical, and Stryker.

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