Treatment of the postmeniscectomy knee with unicompartmental osteoarthritis remains a challenging clinical problem. Despite pharmacologic advances and surgical innovations, finding the ideal strategy for the patient with single-compartment degenerative disease can be complicated. These patients are generally younger, more active, and have higher expectations. The demands imposed after treatment are generally going to exceed those placed by their older joint replacement counterparts. Complicating this problem is the fact that much of the information we have regarding pharmacologic, physical therapy, and arthroscopic treatments have been directed to the more generalized condition of osteoarthritis. Such information might not be accurately extrapolated to this somewhat different population. However, with that constraint in mind, let us explore the alternative strategies available in managing the postmeniscectomy arthritic knee.

Osteoarthritis affects approximately 16 million Americans, and its cost of treatment represents an estimated 1.5% of the Gross National Product. Nearly 50% of patients over the age of 65 report arthritic symptoms, whereas 70% demonstrate radiographic changes. In 1994, osteoarthritis eclipsed heart disease as the leading cause of disability in the United States.

Arthroscopic meniscectomy is the most common orthopedic procedure performed in the United States, with an estimated 750,000 procedures annually. Many of these patients will later develop osteoarthritis in the operative knee. Exactly how many, however, is a difficult question. There is some literature to suggest that the rate of radiographic degeneration is relatively high, even for partial meniscectomies. Bolano demonstrated a 50% incidence of Fairbanks’ changes on radiographs in a group of 29 patients after partial meniscectomy at 5 years. In 1995, Rangger reported arthritic changes in 38% of patients after medial meniscectomy and 24% after lateral meniscectomy. The rate of degenerative change after subtotal or complete meniscectomy is even higher, with Jorgensen et al. demonstrating a 40% incidence of osteoarthritis at 4.5 years and 89% at 14.5 years. Subjective results, however, have not always correlated with radiographic findings. Many patients remain asymptomatic despite these reported radiographic changes. Therefore, although we are certain that the absence of the meniscus is associated with degenerative changes, the relationship is not linear and many of these patients do not develop symptoms.

NONOPERATIVE TREATMENTS

Many nonoperative treatment alternatives are available to help manage these patients. Simple measures include lifestyle changes such as activity modification (eliminating provocative, impact-loading activities), weight loss (which can decrease joint reaction force), and physical therapy (which can improve flexibility and strength).

Orthoses

Neoprene sleeves (DuPont, Wilmington, DE) have been reported in the literature to be effective at relieving symptoms in some patients with knee complaints. Scientific evidence of their benefit is lacking, although recent data suggest their value could lie in the en-
hancement of proprioceptive feedback. In general, they represent no more than a treatment adjunct. Semirigid braces could be suitable for patients with mild to moderate unicompartmental osteoarthritis. Through the “three-point bending” principle, “unloader” braces can reduce symptoms by “unloading” the affected compartment through the application of a valgus (medial compartment osteoarthritis) or varus (lateral compartment osteoarthritis) stress.

Several studies have demonstrated their efficacy in decreasing pain and improving function. Potential benefits of bracing include the avoidance of surgery and its costs and complications, including protracted rehabilitation.

The cost of custom bracing can be an issue; however, many durable medical equipment policies now provide some degree of coverage. Another relative disadvantage of bracing is that they can be cumbersome to fit properly, particularly in short, large, conically shaped thighs; are inconvenient to wear; and require absolute compliance to achieve maximum benefit. Careful consideration must be given to proper patient selection.

Some authors have recommended heel wedges, which theoretically decrease pressure on the knee by altering foot and ankle alignment. There is little data to support their effectiveness in patients with osteoarthritic knees. Some authors have suggested a possible adverse effect on ankle function.

Pharmacologic Treatments

Pharmacologic treatments include both oral and injectable medications. Oral medications commonly include acetaminophen, nonsteroidal anti-inflammatories (NSAIDs), and recently popularized “supplements.”

Acetaminophen: Acetaminophen has a well-established safety and efficacy profile, permitting a daily maximum dose of 4,000 mg per day. According to the American College of Rheumatology’s algorithm for the treatment of osteoarthritis, acetaminophen is the first line of therapy after nonpharmacologic modalities.

Nonsteroidal Anti-inflammatory Drugs: Among orthopedists, NSAIDs are usually the first line of treatment. These medications are designed to reduce the inflammation associated with osteoarthritis by inhibiting the production of prostaglandins in the cyclooxygenase (COX) pathway. Two different cyclooxygenase enzymes have been described, known as COX-1 and COX-2, respectively. COX-1 enzymes are responsible for the production of thrombox-
quality and price. Oral supplements are not regulated by the Food and Drug Administration (FDA) and do not fall under their guidelines regarding quality or efficacy. In fact, no agency holds manufacturers accountable to ensure that the contents of the container match those written on the label. Recent studies with a randomly selected group of common supplements found that a significant proportion of these products had no active ingredient.29,30 Adebowele reported on the evaluation of 32 products containing glucosamine and/or chondroitin. He found a shocking 84% failed to meet label claims. Actual concentrations of substances ranged from 0% to 115% of stated values.29 Similarly, Consumer Reports analyzed 19 products and found a wide variety of recommended dosages and a wide range of product concentrations and label claims, some of which were not legitimate. Their report can be found in the May 2002 issue or online (available at www.consumerreports.org). The take-home message here is that as a clinician providing guidance to your patients, it is important to become somewhat conversant with the quality of the products on the market. Recommend that your patients consult the available consumer data and purchase a supplement from a reputable manufacturer whose product claim has been substantiated by independent testing (such as www.consumerlab.com).

The literature is fairly extensive in evaluating the efficacy of chondroitin and glucosamine in animal models and in humans. Unfortunately, this data is often biased by industry support, precluding clear interpretation of the results. Here is what we do know about these 2 potentially important supplements.

Glucosamine sulfate is ubiquitous in the environment and is the monosaccharide precursor to glycosaminoglycans, which are the building blocks of proteoglycan, the large macromolecule that constitutes 5% to 10% of the wet weight of articular cartilage.32 Other glycosaminoglycans include chondroitin sulfate, heparin sulfate, and dermatan sulfate. Glucosamine is extracted from shellfish such as shrimp and crab, which is an important consideration for patients with seafood allergies.33,34 In its sulfated form, glucosamine has a 70% absorption rate in the gastrointestinal tract with a 26% overall bioavailability. It is excreted by the kidneys and is thought to work in a number of ways, including: (1) stimulation of chondrocyte collagen and proteoglycan production, including hyaluronic acid; (2) stimulation of synoviocytes; and (3) mediation of an anti-inflammatory effect through the theorized stabilization of basement membranes and production of intracellular ground substance.35

Chondroitin sulfate is made up of repeating disaccharide units of galactosamine sulfate and glucuronic acid, and is similar in molecular structure to heparin. Its bioavailability is variable, but it is thought to be approximately 70%. Chondroitin is generally derived from cow cartilage. It works by inhibiting degradative enzymes and serving as a substrate for the production of proteoglycans.36

Lipiello et al. have reported a synergistic increase in proteoglycan production and a decrease in degradative enzymes in animals that were administered both glucosamine and chondroitin.36 They also noted a “protective” benefit histologically in those animals administered chondroitin/glucosamine versus placebo.36 Most studies indicate that these 2 products, taken in combination, seem to provide some level of subjective symptomatic improvement, but this benefit could take several months to appear.32 A review of articles through the year 2000 summarized the effectiveness of clinical studies, and found that overall they seemed to be comparable to NSAIDs without the side effects.37 McClendon et al performed a meta-analysis in 2000, analyzing the literature through 1999, finding 17 placebo-controlled trials, 15 of which satisfied their inclusion criteria. Of these 15 trials, 13 had received some element of financial support from product manufacturers. Not surprisingly, they found that these studies exaggerated claims of clinical improvement, were flawed in design, included inadequate numbers of patients, and used nonvalidated outcome measures.37

Subsequent to this report, several additional studies have been published regarding the efficacy of supplements. Two that are of recent interest include those of Reginster et al. and Pavelka et al. In 2001, Reginster reported the results of a randomized, double-blind, placebo-controlled study of 212 patients taking either glucosamine sulfate (alone) or placebo over a 3-year period.38 They reported improvement in WOMAC scores in the glucosamine-treated cohort and a decreased incidence of radiographic changes, making this the first clinical study to suggest a possibility of a real “chondroprotective” benefit. In the second study, Pavelka examined the outcome of 202 patients administered glucosamine sulfate (alone) versus placebo, followed subjectively and radiographically for 3 years.35 Like Reginster, they found better subjective scores and decreased joint space narrowing in the glucosamine-treated group. Although there were limitations in study designs, both of these studies suggest
a possible chondroprotective benefit and lend credence to claims that these agents can, in fact, influence the disease, not merely modify the symptoms.

So do supplements work? Well, in the laboratory and in animal models, they certainly seem to stimulate production of cartilage-building proteins and inhibit degradation by enzymes. However, do they truly provide a protective role? Currently, a large multicenter study jointly sponsored by the National Institutes of Health National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal Skin Diseases is attempting to answer this question. Known as the GCIT (Glucosamine Chondroitin Intervention Trial), this study is intended to test the effectiveness of these supplements in decreasing symptoms and their protective influence on articular cartilage in a large group of patients. Final results are expected in 2005.

Current dosing is weight-dependent, with the recommended daily average dose of 1,500 mg glucosamine and 1,200 mg chondroitin and taken in combination.32,39 Adverse effects include hypersensitivity in patients allergic to shellfish, epigastric pain, heartburn, diarrhea, drowsiness, and skin reactions.35,38 There are no reported effects regarding blood tests such as changes in blood count or serum chemistries.35,38 Structural similarities of chondroitin to heparin sulfate have led to concerns about its use in anticoagulated patients, but no clinical adverse effects have been reported.

Similarly, there have been some concerns about the use of glucosamine in diabetics,40 but there have been no reports of complications. One final report suggested concern regarding the possibility of acquiring "mad cow disease" because some chondroitin is derived from cows. However, no such clinical reports have occurred as a consequence of its use.

Injectables

Cortisone: Injectable medication has been available in the form of corticosteroids for many years and has long been established as an effective, short-term therapy. By inhibiting phospholipase A3, a membrane-associated enzyme that releases arachidonic acid from membrane lipid and initiates the cyclooxygenase and lipoxygenase pathways, corticosteroids transiently decrease inflammation.41,42 Chronic use, however, can actually lead to degenerative changes within cartilage.

Hyaluronic acid: Hyaluronic acid (HA) is a repeating disaccharide unit composed of glucuronic acid and N-acetylglucosamine. It forms the backbone of aggrecan, the large macromolecule that makes up the cartilage matrix. In vivo, it is synthesized by type B synovocytes and fibroblasts and is secreted into the joint space. Most articular HA is composed of approximately 12,500 disaccharide units whose molecular weight is $5 \times 106$ daltons. The healthy human knee contains approximately 2 cc of synovial fluid, with a HA concentration of 2.5 to 4 mg/mL.44 HA has both viscous and elastic properties that are critical to normal joint function. At relatively low load speeds, it acts as a lubricant, and at faster movements it acts as a "shock absorber."43,44 In osteoarthritis, the concentration of HA is reduced by one-half to one-third of normal. The molecular size of HA is also reduced.43,45 This combination leads to decreased effectiveness and increased wear rates, and understandably, raises the possibility that patients could be clinically improved through "viscosupplementation" of HA.

A number of injectable variations of HA have been introduced for the purpose of enhancing normal joint lubrication. They have been approved by the FDA as a "device" rather than a medication. This designation has important implications. As a device, injectable HA was not required to meet the stringent criteria by the FDA for efficacy demanded of drugs in clinical trials.43

The various commercially available preparations of HA are all derived from the fractionated hyalurons from rooster combs. It is thought to lack antigenicity and, once absorbed, is metabolized by the liver. A number of mechanisms of action for HA have been put forth, including anti-inflammatory effects, anabolic effects, analgesic effects, chondroprotective effects, and improved viscoelasticity.43,45

Does it work as a lubricant? Studies have shown a rapid clearance of HA from the joint within 4 days of its administration. Radiolabeling studies show that HA is absorbed by the synovium within 2 hours and in cartilage within 6 hours. In sheep, its mean half-life in normal joints is 20.8 hours and in the acutely inflamed knee only 11.5 hours.46

Despite the relatively rapid metabolism and clearance from the joint, clinical studies show improvement that far outlasts the injectable compound. Such evidence underscores the fact that HA does not exert its predominant clinical effect through viscosupplementation, or simply replacing degraded HA.

Commercial forms vary in their specific composition with respect to the concentration of the HA and the actual molecular form. Formaldehyde has been used to crosslink, and thereby increase, the molecular weight (Hylan G-F 20, Synvisc; Genzyme, Cam-
bridge, MA) in an attempt to more accurately replicate the normal HA molecule. Despite such efforts, with the exception of a single clinical study,\textsuperscript{[47]} little data exists to prove the superiority of large versus small molecular weight HA. Furthermore, the formaldehyde used in crosslinking has been associated with a small incidence of adverse reactions after injection.\textsuperscript{[44,48]}

Animal and human studies have both shown a positive overall benefit to the use of HA in treating mild to moderate OA.\textsuperscript{[49-52]} Animal models have shown some evidence of a chondroprotective benefit. A summary of the clinical literature has been recently published in the Journal of the American Academy of Orthopaedic Surgery.\textsuperscript{43} These studies generally demonstrated subjective improvement when compared with placebo control at 6 months after HA injection. However, no meta-analysis has been published.

Generally, few adverse reactions have been reported (approximately 1%), and those that have occurred have been mild with increased pain, warmth, or swelling at the injection site.\textsuperscript{43} However, one series reported a 27% incidence of a clinically significant inflammatory reaction in 22 patients.\textsuperscript{48} This was attributed to the formaldehyde used in crosslinking the Synvisc preparation. Pricing is variable, depending on the product used, the number of injections required, and the insurance company. Pre-authorization is often required. The injection series can be repeated without apparent limit, with one study showing improvement after each round.\textsuperscript{53} However, a second study demonstrated an increased rate of local reaction with each subsequent series of injections.\textsuperscript{54}

HA is appropriate in patients with osteoarthritis, especially those who are intolerant of other medications and who have failed alternative non-operative strategies. It can be useful in conjunction with other treatments.

**ROLE OF ARTHROSCOPY**

Arthroscopy has long been considered an effective alternative in the treatment of osteoarthritis.\textsuperscript{55-65} However, a recent study by Moseley et al. in the New England Journal of Medicine has called this into question.\textsuperscript{53} In a randomized, double-blind study of 165 Veterans Affairs patients with OA, Moseley found no difference in outcome in groups treated with lavage, debridement, or sham surgery. Their conclusion was that arthroscopy was an expensive and unnecessary modality in the treatment of knee osteoarthritis.

However, some authors have pointed out the limitations of this study, including flawed inclusion and exclusion criteria, insufficient power analysis, and use of nonvalidated outcome measures. They did not provide important information such as body weight, knee alignment, instability, and the presence or absence of knee effusion. Patients with mechanical symptoms (e.g., those most likely to benefit from arthroscopy in practice) were specifically excluded. These criticisms notwithstanding, this study has great value in emphasizing that osteoarthritis patients without mechanical symptoms might not fare as well as we might have thought. This study also highlights the relatively inadequacy of our current scientific database in treating this condition. We need good, prospective, large, double-blind studies to convincingly demonstrate the efficacy of arthroscopy in an appropriately indicated group of patients with osteoarthritis. Clinical variables in the decision-making process should include the presence of mechanical symptoms, alignment, body mass, the presence of effusions, activity level, and patient demands. All of these require careful clinical consideration. Prognostic factors influencing outcome in these patients have been recently reviewed by Hunt in the Journal of the American Academy of Orthopaedic Surgery.\textsuperscript{65}

**SUMMARY**

Management of the unicompartmental osteoarthritic knee is challenging. Recent treatment modalities, including NSAIDs, supplements, and injectable HA, have provided clinically effective adjuncts. Supplements seem to be most effective in treating mild to moderate OA. Wide product variability mandates familiarization by healthcare providers. The widely advertised “chondroprotective” benefit has not been convincingly proven and awaits further outcome studies. Hyaluronic acid seems to be clinically effective in patients with mild to moderate osteoarthritis and has a low complication rate. Its effectiveness, however, is probably not achieved through its marketed “visco-supplementation” mechanism. Further research will allow us to better determine its exact placement in the treatment of osteoarthritis. In the future, the treatment of osteoarthritis will most likely focus on prevention, and biologic manipulation such as gene therapy may eventually render even today’s “advanced” therapeutic alternatives obsolete.
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