Osteoarthritis: New Insights

Part 2: Treatment Approaches

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Osteoarthritis is the most common form of arthritis, affecting millions of people in the United States. It is a complex disease whose etiology bridges biomechanics and biochemistry. Evidence is growing for the role of systemic factors, such as genetics, diet, estrogen use, and bone density, and local biomechanical factors, such as muscle weakness, obesity, and joint laxity. These risk factors are particularly important in the weight-bearing joints, and modifying them may help prevent osteoarthritis-related pain and disability. Major advances in management to reduce pain and disability are yielding a panoply of available treatments ranging from nutriceuticals to chondrocyte transplantation, new oral anti-inflammatory medications, and health education. This article is part 2 of a two-part summary of a National Institutes of Health conference that brought together experts in osteoarthritis from diverse backgrounds and provided a multidisciplinary and comprehensive summary of recent advances in the prevention of osteoarthritis onset, progression, and disability. Part 2 focuses on treatment approaches; evidence for the efficacy of commonly used oral therapies is reviewed and information on alternative therapies, including nutriceuticals and acupuncture, is presented. Biomechanical interventions, such as exercise and bracing, and behavioral interventions directed toward enhancing self-management are reviewed. Current surgical approaches are described and probable future biotechnology-oriented approaches to treatment are suggested.

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There is no known cure for osteoarthritis, and the goal of contemporary management of the patient with osteoarthritis remains control of pain and improvement in function and health-related quality of life with avoidance, if possible, of therapeutic toxicity. Recent studies have demonstrated the potential of treatments ranging from newly approved oral medications to nutriceuticals, patient education interventions, and surgery. Increasingly, appropriate treatment of osteoarthritis combines one or more oral agents with exercise and other biomechanical techniques.

This article is part 2 of a two-part summary of a National Institutes of Health (NIH) conference, "Stepping Away from OA: Prevention of Onset, Progression, and Disability of Osteoarthritis." The conference brought together experts from diverse backgrounds and provided a multidisciplinary and comprehensive summary of recent advances in the prevention of osteoarthritis onset, progression, and disability. For research questions and opportunities identified at the conference, see www.nih.gov/niams/reports/oa/oareport.htm (accessed on 25 May 2000).

SYSTEMIC AND TOPICAL TREATMENTS

Dr. Marc C. Hochberg (University of Maryland School of Medicine, Baltimore, Maryland), Dr. Timothy McAlindon (Boston University School of Medicine, Boston, Massachusetts), and Dr. David T. Felson (Boston University School of Medicine): Drug therapy for pain management is most effective when combined with nonpharmacologic strategies (1, 2). In 1995, the American College of Rheumatology issued guidelines for the medical management of osteoarthritis of the hip and knee (2, 3). Since then, several systematic reviews of drug therapy for osteoarthritis have been published (4–6). The following recommendations for systemic and topical treatments (except for glucosamine and chondroitin, which were not evaluated) are derived from updated recommendations of the American College of Rheumatology for the treatment of osteoarthritis.

Systemic Treatments

Nonopioid Analgesics

For many patients with osteoarthritis, the relief of mild to moderate joint pain afforded by the simple anal-

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gesic acetaminophen is comparable to that achieved with a nonsteroidal anti-inflammatory drug (NSAID) (7, 8). Accordingly, although acetaminophen fails to adequately relieve pain in many patients, it merits a trial as initial therapy on the basis of its overall cost, efficacy, and toxicity profile (9, 10). The daily dose of acetaminophen should not exceed 4 g. Although it is one of the safest analgesics, acetaminophen can be associated with clinically important adverse events, such as prolongation of the half-life of warfarin (11). At therapeutic doses acetaminophen rarely causes hepatic toxicity, but it should be used cautiously in patients with existing liver disease and avoided in patients with chronic alcohol abuse because of known increased risk in these patients (12–14). Even though acetaminophen was reported to be weakly associated with end-stage renal disease, the Scientific Advisory Committee of the National Kidney Foundation recommended it as the drug of choice for analgesia in patients with impaired renal function (15).

Tramadol, a centrally acting oral analgesic, is a synthetic opioid agonist that inhibits reuptake of norepinephrine and serotonin. It has been approved by the U.S. Food and Drug Administration for treatment of moderate to severe pain and can be considered for use in patients in whom acetaminophen therapy has failed and who have contraindications to NSAIDs, including the cyclooxygenase-2 (COX-2)–specific inhibitors. Although numerous studies have examined use of tramadol to treat general pain, few controlled studies have examined its use in osteoarthritis. The efficacy of tramadol has been found to be comparable to that of ibuprofen in patients with hip and knee osteoarthritis (16), and it is useful as adjunctive therapy in patients with osteoarthritis whose symptoms were inadequately controlled with NSAIDs (17). Daily doses of tramadol have generally been in the range of 200 to 300 mg given in four divided doses. Side effects are common and include nausea, constipation, and drowsiness. Despite the opioid pharmacology of tramadol, a comprehensive surveillance program has failed to demonstrate significant abuse, and tramadol remains an unscheduled agent. Seizures have been reported as a rare side effect, either at doses above the recommended range or at doses within the recommended range in patients with a history of epilepsy and those taking concomitant medications that lower the seizure threshold.

NSAIDs

For patients who do not obtain adequate symptom relief with nonopioid analgesics, use of NSAIDs should be considered. The choice between a nonselective NSAID and a COX-2–specific inhibitor should be made after evaluation of risk factors, particularly for upper gastrointestinal and renal toxicity. Data from epidemiologic studies show that among persons 65 years of age or older, 20% to 30% of all hospitalizations and deaths due to peptic ulcer disease were attributable to therapy with NSAIDs (18–20). Furthermore, the risk for a catastrophic gastrointestinal event in elderly patients taking NSAIDs is dose dependent (18). Risk factors for upper gastrointestinal bleeding in patients treated with NSAIDs include age 65 years or older, history of peptic ulcer disease or previous upper gastrointestinal bleeding, concomitant use of oral corticosteroids or anticoagulants, and possibly smoking and alcohol consumption (21–23). Risk factors for reversible renal failure in patients with intrinsic renal disease who are treated with NSAIDs include age 65 years or older, hypertension or congestive heart failure, and concomitant use of diuretics and angiotensin-converting enzyme inhibitors (24). Additional considerations involved in a practitioner's decision to treat an individual patient with osteoarthritis include existing comorbid conditions and concomitant therapy, as well as the side effects and costs of specific treatments.

The options for medical management of the patient with osteoarthritis who is at increased risk for a serious adverse upper gastrointestinal event, such as bleeding, perforation, or obstruction, are use of a COX-2–specific inhibitor or a nonselective NSAID with gastroprotective therapy. Two COX-2–specific inhibitors, celecoxib and rofecoxib, have been approved by the U.S. Food and Drug Administration for use in patients with osteoarthritis (25, 26). Celecoxib has been found to be more effective than placebo and as effective as naproxen for symptoms in patients with hip or knee osteoarthritis (27–29). Rofecoxib has also been found to be more effective than placebo and is comparable in efficacy to both ibuprofen and diclofenac in patients with hip or knee osteoarthritis (30, 31). Endoscopic studies have shown that celecoxib and rofecoxib are associated with an incidence of gastroduodenal ulcers lower than that of comparator NSAIDs and similar to that of placebo (25). These data suggest an advantageous safety profile compared with nonselective NSAIDs, especially for treatment of high-risk patients (21–23). However, no large long-term studies have been published that were designed to demonstrate differences between COX-2–specific inhibitors and nonselective NSAIDs with respect to major gastrointestinal clinical outcomes; such studies are in progress.

A further advantage of COX-2–specific inhibitors with respect to upper gastrointestinal bleeding is that celecoxib and rofecoxib do not have a clinically significant effect on platelet aggregation or bleeding time. In addition, at doses recommended for treatment of osteoarthritis, these drugs appear to be better tolerated than comparator nonselective NSAIDs, with a lower incidence of dyspepsia and other gastrointestinal side effects. As with nonselective NSAIDs, however, COX-2–specific inhibitors can cause renal toxicity. Caution must be exercised, therefore, if these drugs are used in patients with mild to moderate renal insufficiency, and they should not be used in patients with severe renal insufficiency. In addition, celecoxib is contraindicated in patients with a history of allergic reaction to a sulfonamide.

The alternative to use of a COX-2–specific inhibitor is use of a nonselective NSAID with a gastroprotective agent, an approach endorsed by the American College of Gastroenterology (23). As noted earlier, serious adverse upper gastrointestinal events attributed to NSAIDs in the elderly are dose dependent. Therefore, if nonselective NSAIDs are used, therapy should be begun at low, analgesic doses and increased to full anti-inflammatory doses only if lower doses do not provide adequate relief of symptoms. In a study of 8843 patients with rheumatoid arthritis, misoprostol at a dosage of 200 μg four times daily reduced the incidence of serious ulcer complications, including perforation, bleeding, and obstruction, by 51% (32). In a 12-week randomized, double-blind, placebo-controlled endoscopy study, misoprostol at a dosage of 200 μg three times per day had comparable efficacy in prevention of both gastric and duodenal ulcers; however, 200 μg twice daily conferred significantly less protection against gastric ulcers (33). Side effects, particularly diarrhea and flatulence, may occur with this agent in a dose-dependent manner (33). Alternative approaches to prophylaxis with misoprostol include use of omeprazole or high-dose famotidine, both of which have been shown in carefully conducted endoscopy studies to be effective in treating and preventing NSAID-induced gastropathy (34–37). Histamine-2 blockers in usual doses, however, have not been found to be as effective as misoprostol (36), whereas omeprazole (20 mg/d or 40 mg/d) was as effective as misoprostol (200 μg twice daily) in treatment of existing ulcers and was better tolerated and associated with a lower rate of relapse (37). Of note, proton-pump inhibitors have not been approved by the U.S. Food and Drug Administration for use as prophylaxis, although they are being widely used for that purpose.

In addition to their effects on the gastrointestinal mucosa, nonselective NSAIDs inhibit platelet aggregation, further increasing the risk for gastrointestinal bleeding. Nonacetylated salicylates (such as choline magnesium trisalicylate and salsalate) do not produce the antiplatelet effects or renal toxicity associated with nonselective NSAIDs (38) and can also be considered in management of high-risk patients; however, ototoxicity and central nervous system toxicity at clinically efficacious doses may limit their use.

Opioid Analgesics

Patients who do not respond to or cannot tolerate tramadol and NSAIDs and continue to have severe pain may be considered candidates for opioid therapy (1). Tolerance, dependence, and adverse effects, including respiratory depression and constipation, may occur with opioid use.

Glucosamine and Chondroitin

The idea that administration of glucosamine or chondroitin sulfate might have therapeutic effects in treating osteoarthritis by providing substrate for reparative processes in cartilage has been around since at least the 1960s. These compounds occur naturally in the body and may be involved in the repair and maintenance of normal cartilage. They have been used for many years in veterinary medicine for relief of arthritis symptoms. Recently, health and nutrition stores, news shows, and popular books have promoted the use of glucosamine and chondroitin sulfate to treat arthritis, and these products appear to be gaining popularity among consumers.

Interest in these compounds has been tempered by lack of a plausible mechanism to explain how they might achieve a therapeutic effect. Recent laboratory studies indicate that they are absorbed from the gastrointestinal tract (39, 40) and appear to be capable of increasing proteoglycan synthesis in articular cartilage (41, 42). Chondroitin sulfate can increase messenger RNA synthesis by chondrocytes (43) and may partially inhibit leukocyte elastase, thereby reducing degradation of cartilage collagen and proteoglycans (44–47). Glucosamine and chondroitin sulfate have been tested as treatments for osteoarthritis in numerous clinical trials, most of which have demonstrated favorable effects. Of note, most (if not all) trials were sponsored by a manufacturer of the product.

A meta-analysis and quality assessment of 15 double-blind, randomized, placebo-controlled clinical trials of glu-

cosamine and chondroitin compounds evaluated the efficacy of these agents to treat osteoarthritis (48). All but one of these trials were classified as positive, and the studies collectively demonstrated moderate effects for glucosamine (aggregated effect size, 0.44) and large effects for chondroitin (effect size, 0.78) (**Figure 1**). However, quality scoring (on a scale of 0 to 100, on which 100 was highest quality) showed major deficiencies in descriptions of randomization, blinding, and completion rates. Evidence also suggested publication bias. These methodologic problems are likely at best to lead to exaggerated estimates of benefit. In addition, the trials in the meta-analysis measured symptoms only. Inferences, therefore, cannot be drawn about the potential of these compounds to affect the pathologic progression of osteoarthritis.

High-quality independent studies are needed to test the efficacy of glucosamine and chondroitin sulfate. The NIH is supporting a multicenter randomized, double-blind, placebo-controlled study of patients taking glucosamine alone, chondroitin sulfate alone, glucosamine and chondroitin sulfate together, or placebo. Results are expected to be published in 2004.

Topical Analgesics

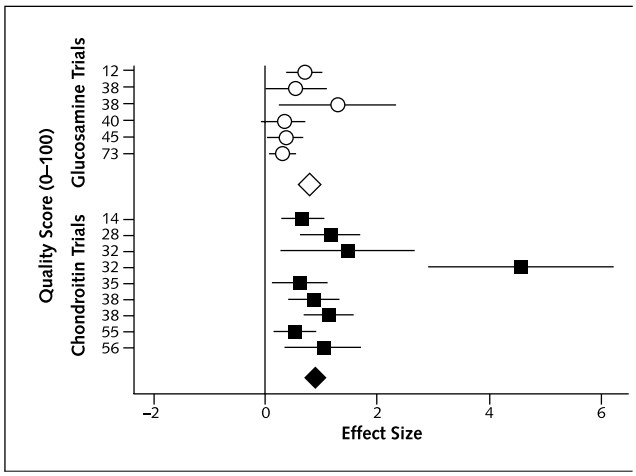
In persons with osteoarthritis of the hand or knee who have mild to moderate pain, use of topical analgesics, such as capsaicin cream, is appropriate as adjunctive treatment or monotherapy (3). A thin film of capsaicin cream should be applied to the symptomatic joint four times daily (49). A local burning sensation is common but rarely leads to discontinuation of therapy.

Treatments Targeted at Altering the Biomechanics of the Joint

Exercise

Dr. Paul A. Dieppe (University of Bristol, Bristol, United Kingdom), Dr. Marian A. Minor (University of Missouri, Columbia, Missouri), and Dr. Steven N. Blair (Cooper Institute for Aerobics Research, Dallas, Texas): Exercise is an effective intervention in osteoarthritis and an important component of primary, secondary, and tertiary prevention. Prolonged inactivity because of osteoarthritis results in poor aerobic capacity and increased risk for cardiovascular disease, obesity, and other inactivity-related conditions (50–52). Furthermore, distention of the knee joint capsule because of fluid accumulation in knee osteoarthritis inhibits quadriceps muscular contraction, leading to decreased strength (53). Evidence is also growing that deconditioned muscle, inadequate motion, and periarticular stiffness may contribute to signs and symptoms of osteoarthritis (54, 55).

Figure 1. **Meta-analysis of placebo-controlled trials of glucosamine and chondroitin in osteoarthritis.**



The white circles represent the effect size of each glucosamine trial; 0 represents no effect relative to placebo. Horizontal lines represent 95% CIs. The white diamond represents aggregate results (with 95% CI) for glucosamine trials. The black circles and diamonds represent the same features for chondroitin. Data from reference 48.

Well-conditioned muscle and muscular balance are needed to attenuate impact loads, provide joint stability, and support function and independence. Muscular conditioning is achieved through well-designed exercise programs performed with supervision or as home exercise routines that incorporate training for strength and endurance at functional speeds and patterns (56–58). Three categories of exercise therapy are used for osteoarthritis: range of motion and flexibility exercise, muscle conditioning, and aerobic cardiovascular exercise. Adequate joint motion and elasticity of periarticular tissues are necessary for cartilage nutrition and health, protection of joint structures from damaging impact loads, and function and comfort in daily activities. Exercise to regain or maintain motion and flexibility is achieved by routines of low-intensity, controlled movements that do not cause increased pain (59, 60). Clinical trials have provided strong evidence of the efficacy of muscle conditioning and aerobic exercise to lessen symptoms in persons with osteoarthritis of the knee (61–63).

More generally, reports in the past few years from the NIH (64), the Centers for Disease Control and Prevention/American College of Sports Medicine (65), the U.S.

Surgeon General (66), and the American Heart Association (67) have concluded that a fit and active way of life provides numerous health benefits and that physical inactivity is an important public health problem in the United States, one that is especially relevant to those with osteoarthritis. The benefits of activity include reduced risk for several chronic diseases, increased longevity, improved psychological health, and enhanced quality of life (64–67). Important components of quality of life are preservation of function and reduction in disability associated with musculoskeletal diseases and conditions (66).

Bracing and Footwear

Bracing and corrective footwear have mainly been used to treat osteoarthritis of the knee but not the hip. There are good theoretical grounds for use of such interventions: Shock-absorbing footwear reduces damaging impact loading (68), heel wedging reduces lateral thrust on the knee (69), support sleeves increase proprioception and reduce overall feelings of instability (70), dynamic bracing controls lateral instability (71), and taping allows repositioning of the patella (72). These methods are cost-effective and simple alternatives to more complex or expensive interventions.

A review of the literature (73) has shown that very few studies of bracing and footwear have been published and that most of them are not randomized, controlled trials. However, the trials that have been undertaken indicate good symptom relief (70–74), and it has been suggested that heel wedges are an alternative to knee replacement for medial tibiofemoral osteoarthritis (75, 76).

Acupuncture

Dr. Brian M. Berman (University of Maryland School of Medicine, Baltimore, Maryland): In 1997, a national survey showed that 26% of persons with self-reported arthritis had used a complementary and alternative therapy in the past 12 months, a significant increase since 1990 (77). A survey of rheumatology patients in the same year indicated that nearly two thirds use complementary and alternative therapies; those with osteoarthritis are the most frequent users (78). Many patients used more than one type of complementary and alternative therapy, and at least half did not tell their physicians. Common reasons given for use of complementary and alternative therapy are dissatisfaction with conventional medicine and feelings that it is ineffective (78, 79). Alternative treatments used included herbs, nutrition, mind–body interventions, homeopathy, manual healing, bioelectromagnetic therapy, and acupuncture. The current data are insufficient or inadequate to permit recommendations on the use of devices, such as bioelectromagnetic fields and magnets or nutritional interventions (including herbs). The remainder of this section therefore focuses on acupuncture.

Basic science research suggests that acupuncture relieves pain through activation of the gate-control system, in which large nerve fibers are stimulated and suppress small fibers that transmit signals in the dorsal horn of the spinal cord (80, 81), or through release of neurochemicals in the central nervous system (82–87). Several clinical trials have been conducted in the United States and Europe on the effectiveness of acupuncture for osteoarthritis (88–96). Many of the studies have compared acupuncture with sham acupuncture or inert placebo (for example, mock transcutaneous electric nerve stimulation). Although these trials have shown significant improvement in pain scores, no significant between-group differences were found (88–92). Results of a systematic review of the literature by Ernst (97) were generally inconclusive; seven of the included studies reported positive results for acupuncture treatment and six reported nonsignificant results. Overall, the methodologic quality of the trial designs was poor, including small samples and failure to control for placebo effects. Two more recent, larger trials (96, 98), however, have suggested efficacy of acupuncture under controlled conditions, one of which involved a sham acupuncture control (98); this finding raises the possibility that the negative results obtained previously were a function of small samples (99).

Thus, the research to date on the efficacy of acupuncture in osteoarthritis is inconclusive but promising. A large NIH-funded multisite clinical trial (570 persons), due to be completed in June 2001, is evaluating the efficacy, safety, and cost-effectiveness of acupuncture for osteoarthritis.

Behavioral Interventions

Dr. James F. Fries (Stanford University School of Medicine, Palo Alto, California), Dr. Morris Weinberger (Indiana University, Indianapolis, Indiana), and Dr. Kate R. Lorig (Stanford University School of Medicine): Controlled, randomized trials of behavioral interventions—notably telephone, mail-delivered (100), and group self-management programs—have established major new be-

havioral and social therapeutic interventions as safe and effective in treatment of osteoarthritis. In addition, adherence to such treatments as medications and exercise may be reinforced by telephone-based interventions.

Individualized Telephone-Based Interventions

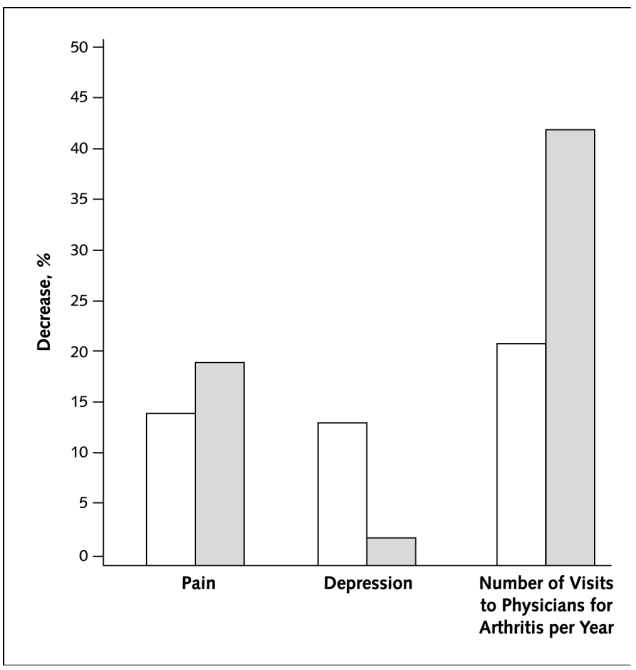
Telephone-based strategies offer many attractive features for delivering sociobehavioral interventions for patients with osteoarthritis. First, telephones are ubiquitous: More than 95% of U.S. residents have telephones in their homes. Second, telephone-based strategies may overcome literacy and language barriers, as well other access problems (for example, they can reach homebound patients). Finally, because they can be used at times that are convenient for patients and providers, telephone-based programs can overcome pragmatic obstacles to education that exist in busy outpatient settings (such as those related to space and time) (101).

Telephone-based programs can be an effective adjunct to care for patients with osteoarthritis. Investigators have evaluated telephone calls by non–health care professionals to review patients' medications, symptoms, and scheduled outpatient visits and to discuss barriers to keeping appointments. Studies with longitudinal (102) and experimental designs (103, 104) have demonstrated clear benefit in terms of patients' functional status and need for subsequent health care and show that telephone-based programs can be delivered at very low cost (105). Of note, the same intervention delivered during regularly scheduled clinic visits had no benefit and even resulted in worse physical functioning. In an extension of this research, counselors used standardized scripts to initiate telephone-based, nondirective counseling. Telephone counseling, but not symptom monitoring, had beneficial effects for patients with osteoarthritis (106).

Group Programs

Patient education is a cornerstone of the treatment of osteoarthritis. Data suggest that group patient education for people with osteoarthritis improves health status and is cost effective (107, 108). Group sociobehavioral interventions produce moderate reductions in pain, the symptom of most concern to persons with arthritis (109). Such programs include patient education content, behavioral change techniques, reciprocal social interaction, and structure based on psychological theory.

Figure 2. **Decreases in pain, depression, and physician visits in 401 patients after 4 months (*white bars*) and 4 years (*shaded bars*) of an arthritis self-management program.**



Pain was measured by using a visual analogue scale in which patients were asked to quantify their current pain. The depression score is derived from Center for Epidemiologic Studies–Depression symptoms scale. Data from reference 107.

The Arthritis Self-Management Program is one such program. It is a community-taught, peer-led intervention in which patients gain skills and self-efficacy to manage the consequences of their disease. In the late 1970s, the program was developed and evaluated in a 4-month randomized trial (110). In several studies conducted over the past 20 years, participants in the Arthritis Self-Management Program reduced their pain by 12% to 19% in the course of 1 month to 4 years ($P < 0.05$ compared with controls) (107, 109, 110). **Figure 2** shows results of one study that showed decreases in pain and visits to physicians for arthritis problems at 4 months and 4 years and a decrease in depression at 4 months (107). In a study of coping strategies, Keefe and colleagues (111), during 10 weeks of group sessions, taught patients and their spouses to cope with osteoarthritis; this strategy reduced pain by 18% ($P < 0.05$ compared with controls).

Patient education programs have also been found to be cost-effective. In a 4-year longitudinal study of the Arthri-

Table. **Selected Preliminary Clinical Results of Cartilage Transplantation**

Treatment	Clinical Application	Trial Results
Osteochondral autograft	Small chondral lesions 10–22 mm in diameter; young patients	Short follow-up (1–5 years); hyaline cartilage observed, but incomplete integration to host; 91% of patients had clinically good or excellent outcome (130)
Osteochondral allograft	Post-traumatic osteoarthritis and traumatic defects of single femoral condyle or tibial plateau; osteonecrosis of distal femoral articular surface	Fresh osteochondral allografts: 75% successful at 5 years, 64% at 10 years (134, 135); frozen osteochondral allografts for distal femoral condyle: 70% successful at 4.2 years (126)
Tissue engineering		
Autologous chondrocyte therapy	Localized defects of femoral condyle; patella 10–12 mm in diameter	Clinical improvement observed in 90% of patients at 2–9 years of follow-up (128)
Undifferentiated mesenchymal cells	Localized chondral defects <2 cm in diameter	Very early clinical application; hyaline cartilage observed at <1 year in biopsy specimens

tis Self-Management Program, visits to physicians by patients with osteoarthritis were reduced by 39%, for net savings of approximately $189 per participant (1987 U.S. dollars) (107). In a randomized trial, Cronan and colleagues (108) found a savings of $1156 dollars per patient per year after participation in a group patient education intervention. These savings are based on significantly fewer days spent in the hospital.

Sociobehavioral interventions are more effective than informational programs in decreasing pain (109). Several studies in the past 15 years have suggested that self-efficacy, or confidence, is one of the mechanisms by which patient education and sociobehavioral interventions improve health status (107, 109–111). In the Spanish-language version of the Arthritis Self-Management Program (112), baseline self-efficacy and improvements in self-efficacy from baseline to 4 months were significant predictors of less pain at 1 year ($P < 0.01$).

Despite results showing that sociobehavioral interventions in people with osteoarthritis improve health status and are cost-effective, less than 2% of the U.S. population with osteoarthritis has participated in these interventions. One reason is that these interventions have been implemented largely outside the health care system. Until sociobehavioral interventions are incorporated into medical care, their benefits may go largely unrealized.

Surgical Treatment of Osteoarthritis: Current and Future Approaches

Dr. Joshua J. Jacobs (Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois) and Dr. Victor Goldberg (Case Western Reserve University, Cleveland, Ohio): In the vast majority of cases, surgical treatment of osteoarthritis is considered only after failure of nonsurgical treatments. Four categories of nonbiological procedures are considered surgical management: osteotomy, arthroscopy, arthrodesis, and arthroplasty. Osteotomies are performed in persons with early osteoarthritis and may relieve symptoms and slow the rate of progression (113). Arthroscopic debridement and lavage can also successfully alleviate symptoms, particularly in the case of degenerative meniscal tears in the presence of mechanical symptoms. However, when there is substantial joint-space narrowing, arthroscopic surgery has limited benefit.

Arthrodesis, or joint fusion, successfully alleviates pain and is commonly performed in the spine and in small joints of the carpus, hand, and foot. Arthrodesis of the major proximal joints of the upper and lower extremities is not well tolerated because of the major functional deficits associated with loss of motion. In the hip and knee, arthrodesis is reserved for the very young patient with unilateral disease or as salvage therapy.

Total joint arthroplasty represents the most significant advancement in the treatment of osteoarthritis in the past century. It is the mainstay of surgical treatment of the osteoarthritic hip, knee, and glenohumeral joint. For most persons, especially elderly ones, total joint replacement is a highly successful procedure that will probably last for the duration of their lives (114–116). By all measures, total joint replacement is among the most effective of all medical interventions; the pain and disability of end-stage osteoarthritis can be eliminated, restoring patients to near-normal function (117, 118). This operation is also highly cost-effective (119).

Total joint replacement has limited durability in persons with life expectancies exceeding 20 years and those

who wish to participate in high-demand activities. The most common reasons for failure of joint replacement that may lead to revision surgery are aseptic loosening and osteolysis, processes that are time- and activity-dependent (120). Osteolysis and aseptic loosening result from the interaction between corrosion and wear debris generated from the implant materials and the cells (macrophages, fibroblasts, osteoblasts, and osteoclasts) within the periprosthetic environment (121, 122). To improve the longevity of joint reconstructions, intense research activity is focused on developing more wear- and corrosion-resistant materials. In addition, great strides have been made in our understanding of the local cell response, producing optimism that further research will yield therapies that will mitigate the adverse host response to prosthetic debris (123).

Recently, biological approaches to the surgical treatment of osteoarthritis have been explored. However, the repair of articular cartilage remains elusive, and the statement by Hunter in 1743 (124) that "ulcerated cartilage is a troublesome thing, once destroyed is not repaired" remains true today. Biological restoration of articular cartilage loss can be approached using two different treatment strategies (125, 126). In the first approach, the resident hyaline cartilage is stimulated to repair the defects by mechanical means, such as osteotomy, or by biological enhancement of bone marrow progenitor cells or growth factors. In the second approach, cartilage transplantation, the articular cartilage is replaced with adult tissue or cells (127, 128).

Three types of cartilage transplantation are available: osteochondral autografting, osteochondral allografting, and use of tissue engineering to transplant committed differentiated chondrocytes (128) or undifferentiated chondroprogenitor cells placed in a supportive carrier to repair osteochondral defects (126, 127, 129) (**Table**). Tissue engineering is still in its infancy, and only preliminary experimental and clinical studies are available.

Osteochondral autografts are currently used clinically to replace small defects (132, 133). Osteochondral allografts have been widely used to replace large, traumatic femoral osteochondral defects; however, the long-term success of these grafts has not yet been determined (130, 131, 134, 135). Osteochondral autografting and allografting may be effective, but, in general, grafting does not appear to be applicable for most joints with osteoarthritis, a situation in which articular cartilage defects are often too large for this approach to be successful.

Finally, tissue engineering of biologically active cells, signal molecules, and a biomatrix to assemble functional tissues and organs are promising biological treatments (125, 127). Early clinical and experimental results of autologous chondrocyte therapy suggest that approximately 90% of patients experience clinical improvement (128). However, the long-term durability of this treatment approach remains in doubt. Another approach has been to use undifferentiated mesenchymal cells in a supportive biomatrix. Early experimental studies suggest that these cells are capable of synthesizing adult functional hyaline cartilage (129). However, additional studies are needed to address the ideal combination of cells, biomatrices, and growth factors to provide an effectively tissue-engineered articular surface for long-term successful function.

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