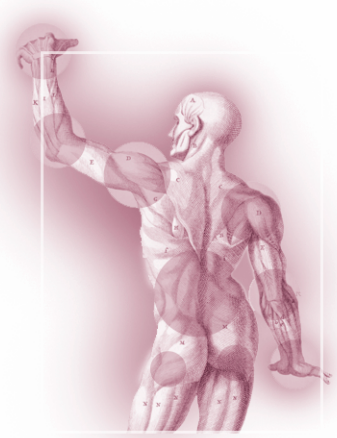

Osteoarthritis

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Arthritis is a common, disabling condition that affects an increasing percentage of the population. This article includes discussion of new theories of risk factors and treatment paradigms.

(Key words: osteoarthritis, pain, joint injury)

Arthritis is one of the most common chronic debilitating diseases in the United States. Age is the most powerful risk factor for the development of osteoarthritis, which is the most common form of arthritis affecting Americans. Osteoarthritis affects more than 21 million people in the United States,[1] and radiography-demonstrated changes of osteoarthritis occur in a majority of individuals by age 65 years and are seen in more than 80% of persons older than 75 years.[2] Because the US population is growing older, the prevalence of osteoarthritis is increasing as well. Only 4% of the population in the United States was older than 65 years in 1900, but by the year 2030, 22% of the US population will be older than 65. Therefore, by the year 2020, more than 50 million persons in the United States will be affected by arthritis, which will increase the direct and indirect dollars spent on arthritis care by more than 25%. More than one third of the US expenditure on healthcare in the United States in 1996 was devoted to providing care for individuals older than 65 years.[3] Healthcare expenditures rise as individuals age. More than 40% of persons older than 85 years require assistance with their activities of daily living and an increasing number of services that are offered in long-term care facilities. Osteoarthritis is the most common reason for total hip and total knee replacement.

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Risk factors

Age

Osteoarthritis causes symptoms in approximately 12% of US adults between the ages of 25 and 74 years. The increased incidence of osteoarthritis occurs most among women older than 45 years.[4] Before the age of 50 years, the problems of osteoarthritis in most joints is higher in men than in women, but after the age of 50 years, women are more affected, usually in their hands, feet, and knees, than men.

Osteoarthritis can be defined either by symptoms, radiographic findings, or by an underlying pathologic process. Osteoarthritis of the hips and knees has the greater clinical impact because these joints are weight-bearing. Osteoarthritis is multifactorial so that risk factors other than simply advancing age may be important (*Figure 1*). There have been associations to obesity, quadriceps muscle weakness, joint overuse or injury, genetic susceptibility, and developmental abnormalities, among others.

Ethnic characteristics

The evidence is conflicting regarding ethnic differences in osteoarthritis of the hip and knee. Although one study has indicated higher rates of knee osteoarthritis in African American women but not men, another study from the rural South suggested no differences in disease prevalence.[5,6] Ethnic differences in the risk of development of osteoarthritis could be explained by differences in body mass index, for example, so other factors may also be important.

Estrogen replacement therapy and bone mineral density

Estrogen replacement therapy (ERT) has been associated with significant reduction in moderate to severe symptomatic osteoarthritis in the hip in white postmenopausal women. Although cohort studies have reported that women taking estrogen have a decreased prevalence in incidence of radiographic findings of osteoarthritis, case-controlled studies have been inconsistent in their findings.[7-9] It may also be that women who are on ERT are in general healthier than women who are not on ERT, and therefore, there may be some confounding because of these healthy habits among women who are hormone users.

There seems to be an inverse relationship between osteoarthritis and osteoporosis in that a higher bone mineral density is associated with an increased prevalence of knee and hip osteoarthritis, whereas women with low bone density and osteoporosis seem to have a decreased incidence of osteoarthritis. The role of estrogen in osteoarthritis is clearly complex.

Nutritional factors

Vitamins and arthritis have been linked for many years. Vitamins A, C, and E are major antioxidants in the diet. They all have been associated in one way or the other with osteoarthritis. Vitamin D may also play a role in osteoarthritis. Nutritional factors play a role in osteoarthritis by either protecting against oxidative damage in the joint, modulating the inflammatory response affecting cellular differentiation within the arthritic joint, or altering biologic actions related to both bone and collagen synthesis.[10] In individuals who have a high intake of vitamin C, there has been an associated decrease in the risk for progressive osteoarthritis as diagnosed on x-ray studies. These individuals have also had less knee pain than individuals who take less vitamin C. Vitamin D may have some direct effect on bone-remodeling cells. Once again, there has been about a threefold increase in the risk involvement of osteoarthritis in persons with low vitamin D intake. No evi-

dence exists, however, that a low dietary intake of vitamin D influences the risk for development of osteoarthritis in someone who has previously had a nonarthritic knee. The low levels of dietary intake of vitamin D are associated with progression of established osteoarthritis of the knee. This role for vitamin D might be attributable to its potential to contribute to the immunologic response and inflammatory products. Vitamin D receptors have been found within arthritic joints.[11] Therefore, dietary levels of vitamin D may be relevant to osteoarthritis.

Unfortunately, people rarely consume each of these vitamins and other nutrients as independent agents. Dietary supplements often contain multiple vitamins and minerals. Therefore, it is difficult to isolate the effect of one vitamin or other nutritional supplement in the etiology or the progression of osteoarthritis.

Genetic susceptibility

A genetic susceptibility to osteoarthritis now appears to be evident in some cases. Up until about 20 years ago, osteoarthritis was thought to simply be due to the degeneration of cartilage within joints. Therefore, medical therapy would have limited benefit because osteoarthritis was simply a mechanical problem. Inflammation is present within osteoarthritic joints.[12] Genetic factors probably account for at least half of all cases of osteoarthritis of the hands and hips. This probability raises the possibility at some point that gene therapy might be an approach to therapy in the future.

Obesity

Obesity is clearly a risk factor for osteoarthritis, especially osteoarthritis of the knee. Felson and colleagues[13] observed that women who lost only an average of 11 pounds were able to decrease their risk of development of osteoarthritis by up to 50%. The relationship between obesity and osteoarthritis of the hip is weaker. A joint can be overloaded simply by the increase in weight. For every step that a person takes, a force of approximately three times one's body weight is transmitted across the knee joint. Therefore, it is easy to see why an increased risk of osteoarthritis occurs in overweight persons.

Obesity is a major problem in the United States, and despite efforts to improve physical fitness in school-age children and adults, the portion of the population considered obese has increased by more than 50% in the past decade.[14]

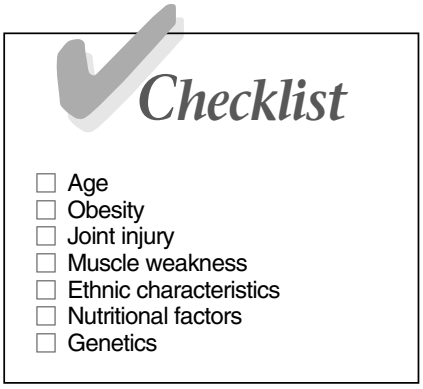

Figure 1. *Risk factors for osteoarthritis.*

Muscle weakness

Muscle weakness also plays a role in the development of osteoarthritis. It is not known whether quadriceps muscle weakness precedes or follows osteoarthritis and whether its cause is diffuse atrophy of the muscles or whether there may be a sensory function of muscle which becomes inhibited and leads to a change in motor function. The knee is the most common joint discussed with regard to muscle dysfunction, primarily because the muscles around the knee are so easily investigated. Muscle has several functions including movement, the maintenance of joint stability, shock absorption, and proprioception. Weak muscles fatigue more quickly, so any dysfunction in muscle would compromise the protective effects and could lead to joint instability, joint pain, and abnormal biomechanical loading on the joint. Over time, this increased stress leads to changes in cartilage and bone consistent with osteoarthritis. Studies have shown that even a relatively small increase in quadriceps muscle strength can result in a significant decrease in the odds of having osteoarthritis of the knee.[15] Criticism of rehabilitation is that even if it is effective, as soon as the exercising stops, then the benefits are lost. Improvement in knee pain and function can certainly occur after exercise programs end.

Joint injury

Congenital dislocation of the hip is associated with an increased incidence of osteoarthritis. In addition, major joint injuries are common causes of osteoarthritis. Jobs with repetitive motion may cause muscle fatigue and therefore increase the risk of osteoarthritis. Jobs that require squatting associated with heavy lifting are associated with high rates of osteoarthritis of the lower extremities. Jobs that require squatting and turning at the same time may cause up to 30% of knee osteoarthritis in men.[16]

Athletic activities can also increase the risk of major bone damage due to repetitive use. Jogging appears to be a minimal risk to the development of osteoarthritis.[17] Other sport activities such as football and soccer put their participants at more risk for knee injuries. Overuse injuries and twisting of joints may also lead to degenerative arthritis such as that seen in baseball pitchers' elbows. Appropriate training to improve joint stability and the use of proper equipment, which would either pad or brace a joint, could potentially decrease these sports-related injuries to a certain degree.

Treatment of patients with osteoarthritis

Because no known cure exists for osteoarthritis, physicians who care for patients with osteoarthritis face difficulties. The increasing burden of disease and disability associated with osteoarthritis presents a significant public health problem. Such treatment certainly needs to decrease pain and improve function, while trying to avoid side effects, if possible. Nonpharmacologic modes of therapy (*Figure 2*), including exercises to improve muscle weakness and strengthen joint laxity, are important. New oral medications to decrease pain and even nutriceuticals are now widely prescribed. Last, surgery is appropriate in selected individuals.

Nonpharmacologic therapy

Nonpharmacologic management of osteoarthritis includes weight loss, education for patient and family, physical and occupational therapy, aerobic conditioning exercises, and the use of appropriate assistive devices such as canes and better footwear to decrease the mechanical stress on joints.

These nondrug treatment modalities may limit the need for analgesic agents, and therefore could potentially spare patients the side effects of drugs. Physical therapy in osteoarthritis includes range-of-motion exercises, muscle-strengthening exercises, and the use of assistive devices. If a person is unable to move a joint through an entire range of motion because of pain, then the prior use of heat will help to stretch tissues and therefore can make it easier to exercise. Quadriceps-strengthening exercises are very important. The Fitness Arthritis in Seniors Trial (FAST)[18] demonstrated that

quadriceps muscle strengthening and aerobic exercise will decrease pain and disability. A recent study by Deyle and associates[19] evaluated the effectiveness of manual physical therapy for osteoarthritis of the knee conducted by physical therapists who had formal training in such treatment. They hypothesized that physical therapy that consisted of manual therapy to the knee, hip, ankle, and lumbar spine combined with traditional range-of-motion muscle strengthening and cardiovascular exercises would be more effective than placebo for improving function, decreasing pain, and increasing functional capacity. Patients were actually evaluated 1 year after completing the study. Although the active portion of the treatment lasted only 8 weeks, there were more knee surgeries in the patients received the placebo than in the treatment group 1 year after the active therapy ended. Therefore, the authors concluded that the patients with osteoarthritis of the knee who were treated with a combination of manual physical therapy and exercise had statistically significant improvements in pain relief and functional ability compared with a placebo group. The effectiveness of this treatment persisted 1 year after the conclusion of this study. The manual therapy consisted of passive physiologic and accessory joint movements, muscle stretching, and soft tissue mobilization primarily applied to the knee. In addition, the treatment group received a standardized knee exercise program at each session.

Pharmacologic treatment

Pharmacologic treatment modalities for osteoarthritis consist of systemic drugs, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, glucosamine, and chondroitin sulfate (*Figure 3*). In addition, there is intra-articular therapy consisting of corticosteroids and hyaluronic acid. Topical therapy is also an option.

For many patients with osteoarthritis, simple analgesics such as acetaminophen offer pain relief comparable to that achieved with an NSAID.[20] In one study, treatment with high doses of acetaminophen was compared to treatment with low and high doses of ibuprofen for 4 weeks. With the exception of pain at rest, no meaningful or significant differences were found between the three treatment groups. Although acetaminophen is safe, it has been associated with some important side effects such as prolongation of the prothrombin time. In large doses, it may be associated with liver toxicity.

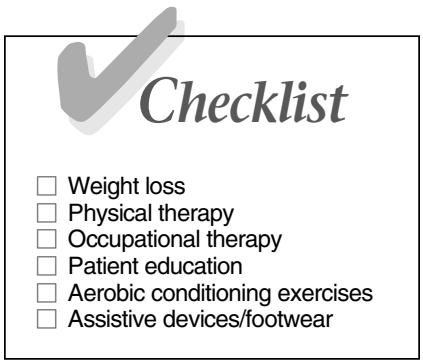

Figure 2. *Nonpharmacologic treatment of osteoarthritis.*

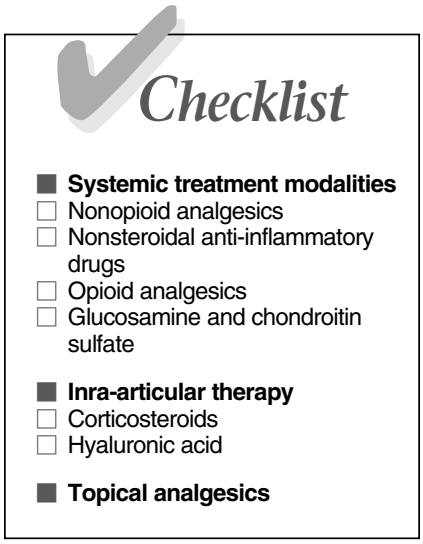

Figure 3. *Pharmacologic treatment of osteoarthritis.*

Tramadol hydrochloride (Ultram) is a synthetic opioid agonist approved for the treatment of moderate to severe pain. Tramadol may be comparable to ibuprofen in the relief of pain of osteoarthritis of the hip and knee.[21] Side effects of tramadol include nausea, constipation, drowsiness, and seizures.

NSAIDs offer relief of pain and inflammation associated with osteoarthritis but also have side effects. Currently, the choice between a nonselective NSAID and a cyclooxygenase-2 (COX-2) specific inhibitor is an option that did not exist before January 1999. Risk factors for upper gastrointestinal bleeding in patients treated with NSAIDs include a history of peptic ulcers, the use of oral corticosteroids or anticoagulants, and age 65 years or older. In addition, comorbid conditions and multiple-drug therapy may pose additional considerations for the use of COX-2 specific inhibitors. Two COX-2-specific inhibitors, celecoxib (Celebrex) and rofecoxib (Vioxx), have been approved for use in patients with osteoarthritis.[22,23]

Two recently published long-term studies have shown differences between COX-2 specific inhibitors and nonselective NSAIDs with respect to major gastrointestinal clinical outcomes.[24,25] Another advantage of rofecoxib and celecoxib is that neither drug has a clinically significant effect on platelet aggregation or bleeding time. At doses recommended for the treatment of osteoarthritis, these drugs appear to be better tolerated than comparative nonselective NSAIDs, and therefore, both have become widely used in the treatment of osteoarthritis. As with nonselective NSAIDs, COX-2 specific inhibitors can cause renal toxicity. In addition, celecoxib is contraindicated in patients with allergic reactions to a sulfonamide.

Alternatively, nonselective NSAIDs can be combined with misoprostol (Arthrotec, Cytotec) or omeprazole (Prilosec). In either case, although there may be a decrease in serious adverse upper gastrointestinal events with these combinations of therapy, platelet aggregation would still be inhibited.

Opioid analgesics can be used for severe pain associated with osteoarthritis unresponsive to acetaminophen, tramadol, or nonsteroidal anti-inflammatory drugs.

Glucosamine and chondroitin sulfate have been used in the treatment of osteoarthritis for more than 40 years. Products are found in both health food stores and pharmacies. They have been purported to decrease the pain of osteoarthritis. A meta-analysis of 15 different studies was recently published.[26] Only controlled studies of at least 4 weeks' duration were analyzed. Fifteen such studies were included, and all but one was classified as positive. The studies demonstrated moderate effects for glucosamine and large effects for chondroitin. The authors concluded that the quality of the studies was poor, and therefore, the methodologic problems could have exaggerated the estimates of benefits. The National Institutes of Health is currently 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 not expected for another 3 years.

Complementary and alternative treatment

In addition to the foregoing list of treatment modalities, use of topical analgesics such as capsaicin cream may be useful to decrease pain in osteoarthritis.

Complementary and alternative therapy is often used in the treatment of osteoarthritis. A recent study of rheumatology patients[27] showed that those with osteoarthritis are the most frequent users of alternative modes of treatment, including mind-body interventions, acupuncture, and manipulative therapy.

Behavioral interventions, specifically telephone-based interventions, are intriguing. Obviously, telephones are found in most households; therefore, studies have shown that a telephone-based program can be used to call patients to check on their symptoms, review medication use, and offer counseling.[28]

Surgical treatment

Last, surgical treatment of osteoarthritis can be considered after failure of all other nonsurgical modes of treatment. Arthroscopic surgery may alleviate symptoms and is probably indicated before substantial joint space narrowing has occurred. Total joint replacement represents a significant advancement in the treatment of osteoarthritis. Total joint replacement is among the most effective of all modes of therapy, particularly for osteoarthritis of the hip and knee.[29] Younger patients may outlive the durability of the total joint replacement, and therefore require revisions of their replaced total joints. Recently, cartilage transplantation has become available. Only preliminary experimental and clinical studies have been done to date.

The prospects for safer and more effective management are better than at any time in the past. Not only are new drugs being developed that will alleviate joint pain in osteoarthritis, but surgical procedures are being developed as well. Nonpharmacologic and nonsurgical treatment of osteoarthritis continues to be a mainstay in the day-to day management of patients with osteoarthritis.

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