Introduction

About 9.6% of the Taiwan population are 65 years of age or older. Osteoarthritis (OA) is the most common form of chronic arthritis, which is a common cause of functional limitation and dependency in the elderly in Taiwan. The age-related changes in muscle strength and knee OA increase susceptibility to falls, which are associated with significant morbidity and mortality in the elderly. The plan for management should be tailored to the individual elderly patient and should be a multidisciplinary approach that includes nonpharmacologic modalities combined with pharmacologic measures. Our understanding of the etiopathogenesis of knee OA has grown significantly in recent decades, which has led to targeted and more effective approaches to disease management. Therapeutic advances include the introduction of safer agents for symptomatic relief, as well as agents with potential for disease or structure modification. [International Journal of Gerontology 2007; 1(1): 31–39]

Key Words: disease-modifying osteoarthritis drug, elderly, knee osteoarthritis, Taiwan, therapy

Risk Factors for Knee OA

OA is a slowly developing multifactorial disorder in which aging, genetic, hormonal, and mechanical factors are major contributors to its onset and progression. The incidence and prevalence of this disease increase directly with age. By the age of 60 years, nearly 100% of the population will have histologic changes of degeneration in their knee cartilage, over 80% will have radiographic evidence of OA in at least 1 joint, about 40% will report having clinical symptoms of arthritis, and about 10% will report activity limitation caused by arthritis. In an elderly cohort in the Framingham OA study (age range, 63–94 years), radiographic knee OA...
was present in 27% of those below 70 years of age, and 44% in those aged 80 years or above\(^\text{11}\). Symptomatic knee OA was less common than radiographic OA, with 7% of those below 70 years of age, and 11.2% of those 80 years or above reporting knee pain on most days for at least a month\(^\text{11}\). The rate of incident radiographic OA of the knee was about 2% per year in women, and progressive disease occurred at 4% per year with approximately 1% per year developing new knee pain\(^\text{11}\).

Previous studies have found that the female sex is associated with an increased risk of OA\(^\text{12,13}\). At 50 years of age, women have higher rates of incident knee OA compared to men\(^\text{14}\), and a higher prevalence of radiographic and symptomatic OA\(^\text{3,15,16}\). The Framingham OA study showed that women had rates of incident disease 1.7 times higher than that in men\(^\text{15}\). Recent epidemiologic studies suggested that postmenopausal estrogen deficiency could play a role in the development of OA in women\(^\text{17–19}\).

After age, obesity is the strongest modifiable risk factor for the development of knee OA, particularly in women\(^\text{10}\). For incident radiographic knee OA in the elderly Framingham group, higher body mass index (BMI) was associated with an odds ratio of 1.6 per 5-unit increase in BMI\(^\text{20,21}\). Weight change also correlated with risk such that an increase in risk of knee OA of 40% was noted per 10-lb weight gain and a similar decrease in risk was noted for weight loss. Among the elderly, the combination of obesity and heavy physical activity is associated with an enhanced risk of knee OA. Data from the Framingham heart study showed that elderly individuals in the upper tertile of BMI who performed at least 3 hours of significant physical activity daily had an odds ratio of 13 for developing knee OA\(^\text{22}\).

A prior history of knee injury is also a risk factor for knee OA\(^\text{15,23,24}\). In a 21-year follow-up of 107 patients who had undergone meniscectomy for management of an isolated meniscus tear, the relative risk of developing radiographic knee OA compared with that of age- and sex-matched controls was 14\(^\text{24}\). Recent studies have also suggested that quadriceps weakness is associated with radiographic and symptomatic knee OA in community-dwelling elderly individuals\(^\text{25}\). In addition, knee proprioception declines with age, and muscle weakness as well as reduced proprioception may contribute to the development of knee OA. These factors could certainly be expected to be involved in the effect of knee OA on physical function\(^\text{26}\).

**Pathobiology of OA**

Pathologically, OA is characterized by fibrillation and loss of articular cartilage, hypertrophic changes in the neighboring bone including subchondral thickening and osteophyte formation, some degree of synovial change with patchy areas of synovitis and areas of hypertrophy, and thickening of the joint capsule\(^\text{27}\). The earliest changes involve roughening of the cartilage surface in areas of the knee joint that receive the greatest stress, such as regions of the tibial condyles not covered by the menisci and vertical ridge of the patella\(^\text{28}\). The morphologic changes become more common and more extensive with advancing age.

The pathobiology of OA is much more complicated than either simple joint aging or wear and tear from repetitive use. OA has traditionally been regarded as noninflammatory arthritis, but improved detection methods show that the inflammatory pathways are upregulated\(^\text{29}\). OA results from articular cartilage failure caused by a complex interplay of genetic, metabolic, and biomechanical factors with secondary components of synovitis. The increased catabolic activity is caused by increased levels of several matrix metalloproteases (MMP), including MMP 1, 2, 8, 9, and 13, and the newly discovered enzyme, aggrecanase\(^\text{30,31}\). Inadequate repair of damaged matrix may be caused by age-related increase in apoptosis\(^\text{32}\), decrease in mitogenic response to insulin-like growth factor-I and other growth factor stimulation with age\(^\text{33,34}\), and decline in proteoglycan synthesis, which has been shown to be correlated with an age-associated increase in pentosidine levels suggesting accumulation of advanced glycation end products\(^\text{35}\). Cytokines and other signaling molecules released from the cartilage, synovium, and bone affect chondrocyte function\(^\text{36}\). Levels of inflammatory cytokines such as interleukin (IL)-1 are increased in OA cartilage and are thought to be important in stimulating catabolism and inhibiting anabolic processes\(^\text{37}\). Age-related changes in the overall composition of the cartilage matrix also result in a tissue that is less able to handle mechanical stress.

Thickening of the subchondral bone, a consistent finding in OA\(^\text{28,39}\), places additional stress on the underlying cartilage during joint loading resulting in mechanical failure of the cartilage\(^\text{40}\). Multiple factors such as body weight, joint stability, and muscle strength influence the rate at which age-related changes result in the development and progression of OA.
Clinical Manifestations of Knee OA

The principal symptom associated with knee OA is articular pain, which is typically exacerbated by activity and relieved by rest. In a more advanced stage of the disease, pain may be noted with progressively less activity, eventually occurring at rest and at night. Articular pain is an important issue in the care of elderly people, and perhaps the most important problem in their daily lives. Morning stiffness is also a common complaint in knee OA patients. It typically resolves less than 30 minutes after patients awaken, but may recur following periods of inactivity. Joint effusions may be present, which typically exhibit a mild pleocytosis and normal viscosity. Limitation of ROM is a common sign of knee OA. In advanced cases, malalignment may be apparent (genu varus or genu valgus), particularly when medial and lateral compartments are affected unequally. A fluctuant swelling along the posterior aspect of the knee, or Baker’s cyst, is also a common complication. The most common clinical problem is differentiation of painful OA from other common causes of regional or generalized joint pain in elderly people, referred pain, periarticular (soft-tissue) conditions, and somatization. The diagnosis of knee OA remains primarily clinical, and the American College of Rheumatology (ACR) has developed classification criteria for this disease to assist the clinician in identifying patients with symptomatic OA.

Management of Knee OA in Elderly Patients

The goals of management of elderly patients with knee OA are to control articular pain and swelling, minimize disability, improve the quality of life, prevent progression of the process, and educate the patient about lifestyle modification. The initial plan for management should be tailored to the individual patient but usually includes nonpharmacologic modalities combined with pharmacologic measures.

Nonpharmacologic modalities

The ACR has recently developed guidelines for the management of knee OA that stress the importance of nonpharmacologic modalities combined with pharmacologic measures. Epidemiologic studies suggested that obesity is strongly associated with the development of elderly OA, so clinicians should encourage their obese patients with knee OA to lose weight. Even moderate weight loss may relieve joint pain, produce improvement in physical function, and reduce progression of OA. Patients can be encouraged by the finding that an average 10-lb weight loss reduced the risk of knee OA by almost 50% in the Framingham cohort. To achieve weight loss in older adults with knee OA, dietary intervention to reduce caloric intake should be recommended.

Given the importance of muscle strength in the pathogenesis of knee OA, exercises to strengthen the quadriceps are particularly important. Individualized strengthening programs developed by therapists have been shown to improve strength and function and relieve pain in subjects with knee OA. Studies have shown that elderly subjects are capable of increasing their quadriceps strength using weights. If available, weight-training equipment, such as a leg extension machine, is beneficial since the weight can more easily be controlled and advanced as the patient improves in strength. The optimal exercise plan may be a combination of lower extremity strengthening exercises and aerobic walking. However, several factors must be considered when creating an individualized exercise program for an elderly patient with knee OA. As an example, a relatively high intensity aerobic exercise program should not be employed for patients with moderate-to-severe OA. The American Geriatrics Society, which supports exercise for elderly OA, has released guidelines for exercise regimens for such individuals.

Patient education and psychosocial support have been shown to relieve pain in OA patients. Patient education should include informative discussions of the disease and of physical disability, therapeutic options, and the risks and benefits of the different approaches to management. Institution of appropriate counseling and antidepressant therapy when indicated are also important issues for the management of elderly patients with knee OA.

There is evidence that physical therapy improves clinical outcome in knee OA. Physical therapists help by developing an exercise program, and occupational therapists provide guidance in using assistant devices.
Physical modalities to improve function can be just as important as those that relieve pain. The application of warm or cold packs to the symptomatic joint can also be helpful. Therapeutic ultrasound has been used to treat knee OA, and is reputed to reduce edema, relieve pain, increase ROM, and accelerate joint tissue repair. Finally, braces and splints may be useful for symptomatic relief for those with knee OA. As an example, valgus bracing of the knee not only reduces pain, but also improves function in patients with OA of the knee that predominantly affects the medial compartment. In patients with more advanced disease, assistive devices such as a cane should be recommended.

**Pharmacologic therapy**

The focus in managing patients with knee OA should not only be centered on pain relief but also on function improvement. When medications are needed, the least toxic drugs should be used for older adults who have increased susceptibility to unwanted side effects. Choices to this end include acetaminophen, non-narcotic analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), topical analgesics, intra-articular corticosteroids, and disease-modifying osteoarthritis drugs (DMOADs).

Acetaminophen has been shown to be as efficacious as NSAIDs in many patients with knee OA. Given its better side effect profile, acetaminophen is a good choice as an analgesic for OA patients, and is the recommended first drug of choice in the ACR guidelines for the management of knee OA and in the guidelines for management of chronic pain in older adults from the American Geriatrics Society. It is important that patients are instructed to use the proper dosage of acetaminophen, which is 1 g 3–4 times a day.

The new ACR guidelines include the non-NSAID analgesic drug tramadol for the treatment of pain associated with knee OA. Tramadol has a dual mechanism of action, binding to the µ-opioid receptor and inhibiting the reuptake of norepinephrine and serotonin. A recently developed drug, Ultracet (tramadol 37.5 mg/acetaminophen 325 mg), is indicated for the short-term management of acute pain in elderly knee OA. In older adults who are at increased risk of side effects from NSAIDs, local treatments should be tried before NSAIDs. Local treatments, including arthrocentesis and corticosteroid injections, are effective for elderly OA patients with synovitis. A general guideline is not to inject the same joint within 6 weeks of a previous injection or more than 3–4 times a year.

If simple analgesics and local treatments in combination with nonpharmacologic agents have not provided adequate pain relief, then NSAIDs may be prescribed. Although widely used in the management of OA, NSAIDs do not provide an obvious advantage over the other types of analgesics but have greater potential for causing serious side effects, particularly in the elderly population. Numerous studies have documented the increased risk of gastrointestinal (GI) ulceration, bleeding, and death in elderly NSAID users. Other potential problems from NSAIDs, which appear more commonly in older adults, include deterioration of renal function and central nervous system (CNS) symptoms, such as confusion, headache, and vertigo. Therefore, indomethacin should not be used to treat older adults with OA because it may exert deleterious effects on the cartilage matrix, seems to be the most toxic of the available NSAIDs, and causes more CNS symptoms than the other NSAIDs. A new class of NSAIDs, the selective COX-2 inhibitors, has less GI toxicity than conventional NSAIDs and provide an alternative choice for elderly patients with knee OA. A cost-effective analysis by Yen et al. showed that among selective COX-2 inhibitors, celebrex was found to be a more cost-effective or even cost-saving strategy if the probability of serious GI complications from conventional NSAIDs was considered. However, COX-2 inhibitors potentially cause vascular thrombosis and heart failure in the elderly population. In patients with known cardiovascular disease or those with multiple risk factors for coronary heart disease, COX-2 inhibitors should be reduced in dosage and duration, or even be avoided. Since the symptoms of knee OA are often intermittent, physicians should try to discontinue NSAIDs when the patient’s symptoms have been stably quiescent. Nonpharmacologic modalities, such as exercise and weight reduction, should be continued.

Topical NSAIDs offer efficacy similar to that of orally administered NSAIDs, reducing some aspects of GI and renal toxicity. However, the efficacy of topical NSAIDs appears to be of relatively short duration. A 2004 meta-analysis, which included 13 trials involving almost 2,000 patients, showed a significant short-term (1–2 weeks) efficacy of topical NSAIDs for pain relief and functional improvement compared to that of placebo. Topical usage of capsaicin (which exerts its therapeutic effect
by enhancing the release of substance P from unmyelinated C nerve fibers) is recommended for patients who do not respond to analgesics or who do not wish to take systemic therapy\(^\text{77}\).

**Disease- or structure-modifying osteoarthritis drugs (DMOADs)**

New therapeutic strategies for treating OA based on present knowledge of its pathogenesis are evolving and a new class of antiarthritis agents, known as DMOADs, has been defined\(^\text{78}\). Clinical research studies are currently underway using other pharmacologic agents that have been shown to favorably slow the disease process in OA.

Tetracyclines have a variety of anti-inflammatory effects that are mediated by inactivation of MMPs, including collagenases, stromelysins, and gelatinases, which degrade all components of the articular extracellular matrix and can cause destruction of articular cartilage\(^\text{79}\). Doxycycline may slow the rate of OA progression. A study showed that the rate of joint space narrowing was significantly less in those treated with doxycycline than in the placebo group\(^\text{79,80}\).

Glucosamine is important for the repair and maintenance of cartilage. A recent in vitro study provided evidence that glucosamine could potentially inhibit the activity of aggrecanase, which is responsible for the cleavage of the large aggregating proteoglycan in cartilage\(^\text{81}\). A 2005 meta-analysis of 20 controlled trials of glucosamine including a total of 2,570 patients with OA\(^\text{82}\) showed that a significant advantage over placebo was noted in the efficacy of glucosamine for pain relief and functional improvement, and there was a modest benefit of glucosamine sulfate on slowing the rate of joint space narrowing. However, a post hoc analysis did not show any significant correlation between the degree of pain relief and the change in joint space width. For patients whose symptoms improve with glucosamine, there is some evidence to suggest that regular use for more than 6 months is no more effective in controlling symptoms of OA than placebo. Adverse effects of glucosamine are not significantly greater than for placebo, but glucosamine should not be administered to patients who are allergic to shellfish.

Chondroitin sulfate is composed of repeating units of galactosamine sulfate and glucuronic acid. It is the predominant glycosaminoglycan found in articular cartilage. A 2003 meta-analysis that involved 755 patients with OA of the knee who were randomly assigned to receive chondroitin sulfate or placebo showed that a significant advantage over placebo was noted in the efficacy of chondroitin sulfate for pain relief\(^\text{83}\). Some trials also had a glucosamine arm, which showed that the efficacy of chondroitin sulfate was similar to that of glucosamine\(^\text{84}\). Despite the promising results noted above, a large double-blind, placebo-controlled randomized trial showed no significant difference in pain relief between those receiving chondroitin sulfate alone or the combination of glucosamine and chondroitin sulfate and those receiving selective COX-2 inhibitor (celecoxib)\(^\text{84}\).

Diacerein is metabolized to rhein, an agent that has anti-inflammatory and analgesic properties\(^\text{85}\). An in vitro study of cultured chondrocytes showed that rhein stimulated prostaglandin E2 synthesis while inhibiting production of IL-1\(^\beta\)\(^\text{86,87}\). A 2006 systematic review of 7 clinical trials that included 2,069 patients with knee OA noted a clinically modest pain relief compared to placebo\(^\text{88}\). Diarrhea was a frequent adverse effect and was reported in those taking diacerein. Another therapy that has been found to relieve pain in knee OA is avocado and soya unsaponifiables (ASU)\(^\text{89}\). They are supposed to stimulate repair of extracellular matrix components, thus enhancing the expression of transforming growth factors \(\beta1\) and \(\beta2\) in cultured articular chondrocytes. The majority of trial data available to date suggest that ASU is effective for the symptomatic treatment of OA\(^\text{90}\). However, the only real long-term trial yielded a largely negative result.

Hyaluronic acid (HA), a major component of synovial fluid (SF) and cartilage, is a high molecular weight polysaccharide made of long nonsulfated straight chains of variable disaccharide lengths composed of \(N\)-acetylglucosamine and glucuronic acid. Its unique viscoelastic properties confer remarkable shock-absorbing and lubricating abilities to SF\(^\text{91}\). In addition, HA can form a pericellular coat around cells, interact with proinflammatory mediators, and bind to cell receptors to modulate cell proliferation and migration\(^\text{91,92}\). It is now believed that biologic activation of multiple protective mechanisms may explain the long-term clinical benefits. A 2005 meta-analysis showed a statistically significant advantage for intra-articular HA injection in rest pain between 2 and 6 weeks when compared to the placebo group\(^\text{93,94}\). Recently, the ACR guidelines have been updated to include recommendations for the use of intra-articular hyaluronans\(^\text{46}\). However, there was no statistically significant difference between those who
received HA injections and those who received oral NSAID (naproxen). Considering the limited resources available for health care in Taiwan, intra-articular HA treatment may not be an economical choice.

When patients with symptomatic knee OA have failed to respond to nonpharmacologic and pharmacologic treatment approaches, surgery should be considered. For those with severe knee OA, joint replacement is very effective.

**Conclusion**

Knee OA is a common and debilitating condition associated with pain and loss of mobility that undermines quality of life in the elderly population. Our understanding of the etiopathophysiology of knee OA has grown significantly in recent decades, which has led to targeted and more effective approaches to disease management. Therapeutic advances include the introduction of safer agents for symptomatic relief, as well as agents with potential for disease (structure) modification. Maintaining or restoring functional capacity in elderly knee OA is an important public health issue. Cartilage replacement by bone marrow stem cells and implantation of autologous chondrocytes or bioengineered tissues continue as important areas of therapeutic interest.

**References**


