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# Management of Early Osteoarthritis

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## Abstract

Osteoarthritis (OA) is a chronic degenerative joint disease of dynamic pathology with multiple etiologies. It involves progressive process of softening, loss of articular cartilage, subchondral bone sclerosis, development of osteophytes, and cyst formation. OA usually contributes to decreased activity associated with aging, secondary to diminished function and pain, thus consequently impairing quality of life. It is well established that pain due to OA, swelling, or stiffness can make it difficult for individuals to perform simple daily living activities. Although OA is not curable, a variety of treatment modalities are available to improve symptoms. Main elements include pain management maneuvers, education, changing lifestyle physical activity (PA), and weight reduction in case of overweight. Although total joint arthroplasty (TJA) is considered a cost-effective treatment for people with OA, TJA should only be considered after failure of conservative treatments. Symptoms of OA are usually managed by either pharmacological or nonpharmacological protocols; joint replacement surgeries are considered in advanced cases. Analgesics remain the keystone of pharmacological treatment for OA symptoms, including paracetamol, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. However, benefits from paracetamol and opioids are minimal, and NSAIDs are not ideal for many patients because they have many side-effects. Intra-articular therapies such as corticosteroids are also commonly used, though usually with short-term benefits.

**Keywords:** early, osteoarthritis, hyaluronic acid, intraarticular

## 1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease of dynamic pathology with multiple etiologies. It involves progressive process of softening, loss of articular cartilage, subchondral bone sclerosis, development of osteophytes, and cyst formation [1].

Knee OA is the most common arthritic disease among all joints; however, there is no available drug treatment today that hinders the progression of this disease process. There are many reasons for this, including the lack of understanding of what worsens the disease process and the heterogeneity of the patient population. There are considerable differences in the course of the disease [2].

The median age for diagnosis of Knee OA is 55 years, and usually people live about 30 years suffering the disease [3]. As there is no known curative treatment for OA till now, treatments aim at improving function as well as reducing pain.

Systematic reviews (SR) are a useful research method to analyze the efficacy of knee OA treatments; however, most of these reviews have not discussed the long-term risks associated with various treatment modalities. The cause for that is most studies follow patients for short time periods. There are missing data in the literature owing to the fact that most of these studies are short-term studies, thus giving a false impression about the correct data concerning short-term improvement; especially, OA is a chronic condition needing long-term studies to correctly estimate the degree of pain improvement.

Approximately 30–65% of the risk of OA is genetically determined [4].

Obesity has long been known as a risk factor for knee OA [3]. A recent meta-analysis also showed that increased BMI added to the increased risks to radiographic and/or clinical OA picture [5].

OA usually contributes to decreased activity associated with aging, secondary to diminished function and pain, thus consequently impairing quality of life. It is well established that pain due to OA, swelling, or stiffness can make it difficult for individuals to perform simple daily living activities [6].

Researches on the role of special diets in OA have been evolving. High dietary fiber intake has been associated with lower risk of developing moderate to severe knee pain over time. Results from two prospective cohort studies also showed that increased total fiber intake was related to lower risk of symptomatic knee OA, but its association with radiographic knee OA is still not evident [7]. Another study found that increased soy milk intake was associated adversely with prevalence of radiographic knee osteophytes [8]. Finally, higher intake of Mediterranean diet was associated with lower prevalence of radiographic and clinical KOA [9].

The patient usually experiences knee pain and any three of the following to diagnose clinical OA of the knee: [1] tenderness on one or more knee compartments; [2] crepitus on active motion in at one or more knee compartments; [3] morning stiffness usually less than 30 minutes, according to WOMAC scale; [4] no warmth on knee examination; [3] age more than 50 years; or [5] osteophytes in one or more knee compartments [10].

Although OA is not curable, a variety of treatment modalities are available to improve symptoms. Main elements include pain management maneuvers, education, changing lifestyle physical activity (PA), and weight reduction in case of overweight. Although total joint arthroplasty (TJA) is considered a cost-effective treatment for people with OA, TJA should only be considered after failure of conservative treatments. Since OA is a chronic disease, a key element in the non-surgical management of knee and/or hip OA is self-management. Self-management interventions allow patients to improve their skills in taking care of themselves and to improve skills to navigate the health care system [11].

The shape of the bone may add to the risk of OA as had been described primarily in the hip joint. The association between OA and muscle strength may vary depending on the muscles and joints being studied. In an examination of anterior cruciate ligament (ACL) injured knees, high thigh muscle cross-sectional area and high muscle/fat ratio had a protective effect against KOA prevalence. Deformities of the knee are a strong predictor of knee OA disease progression [12].

Health education should be considered as a basic element of effective self-management interventions. Health education should include education about OA and its treatment options, exercise and pacing of PA, and weight reduction. This information should be tailored to the person's illness perception and educational capability. In addition, goal setting is a widely used behavioral change technique in many fields, especially in health care. Goal setting is associated with positive impact on behavior at both shorter and longer terms [13]. Behavioral monitoring of outcomes (e.g. amount of PA, weight and achievement of goals).

Symptoms of OA are usually managed by either pharmacological or nonpharmacological protocols; joint replacement surgeries are considered in advanced cases. Analgesics remain the keystone of pharmacological treatment for OA symptoms, including paracetamol, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. However, benefits from paracetamol and opioids are minimal, and NSAIDs are not ideal for many patients because they have many side-effects. Intra-articular therapies such as corticosteroids are also commonly used, though usually with short-term benefits. Pharmacological drugs include the following.

### 1.1 Colchicine

It is usually used for the treatment of pseudogout and gout. Colchicine is not recommended for treatment of OA nowadays. Synovial fluid in OA usually contains basic calcium phosphate (BCP) crystals especially hydroxyapatite crystals (detected in the cartilage of nearly all affected joints at the time of joint replacement surgeries). Positive correlations have been found between synovial fluid BCP crystal levels and radiographic severity of OA [14].

### 1.2 Hydroxychloroquine

Hydroxychloroquine has been used in patients with inflammatory OA of hand joints with some suggested evidence of benefits, probably because it may have a role in treating rheumatoid arthritis (RA) synovitis and an acceptable safety profile. It has immunomodulatory effects and was considered to potentially treat OA due to Toll-like receptor (TLR) signaling inhibition, as TLRs are upregulated in OA cartilage and may have a role in cartilage breakdown *via* proinflammatory pathways [15].

A mixture of pharmacologic and nonpharmacologic therapies can manage OA symptoms as there is currently no available disease-modifying therapy till now, so treatment depends on symptomatic slow-acting drugs for OA (SYSADOAs) as an important category in the pharmacologic therapy tools for OA that have been demonstrated to alleviate the symptoms of functional impairment and pain, with some additional evidence of a disease-modifying effect on the long run [16]. The SYSADOAs class comprises different elements, including chondroitin, glucosamine, diacerein, and avocado soybean unsaponifiables (ASU), and there are some clinical data supporting their efficiency. Placebo-controlled trials of SYSADOAs treatment lasting up to 3 years in more than one Meta-analyses provide evidence that prescribing grade crystalline glucosamine sulfate (GS), chondroitin sulfate (CS), and diacerein has mild to moderate benefits in patients with OA [17].

Numerous meta-analyses and RCTs have been conducted to assess the efficacy and safety of Intra-articular hyaluronic acid (IAHA), with mixed results and conclusions support the fact that IAHA injection is considered a suitable alternative local treatment option providing symptomatic benefit without the systemic adverse effects that may be associated with IA corticosteroids. IAHA is considered to have a positive effect on pain and joint function. A meta-analysis comparing the effectiveness of pharmacological interventions for knee OA found that IAHA is considered an effective therapy. IAHA is also demonstrated to have a longer lasting effect on function and pain compared with IA corticosteroids, lasting up to 6 months [18].

Multiple courses of IAHA can cause long-term beneficial outcomes, including reduction in analgesics used and delay in the need for joint replacement surgeries [19] still found regarding the risk benefit of IAHA. However, controversy about lack of agreement among international guidelines regarding the use of IAHA for the management of symptomatic knee OA still exists [20].



The safety of IAHA has been evaluated in eight meta-analyses of RCTs comparing IAHA to IA placebo. However, a Cochrane review of 76 RCTs was unable to conclude a definitive report on the safety of HA due to limitations concerning sample size; however, no major safety issues were found, in addition, IAHA demonstrated similar efficacy to systemic forms of medical interventions, with more local reactions but fewer systemic adverse effects [21].

Evidence suggests that exercise is one of the core therapies for OA to improve function and pain. The degree of response varies according to the type of exercise (e.g. aerobic, strengthening, etc.). Little is known about the relative efficiency of different exercise forms [22].

The comparisons were seen between strengthening exercises and mixed exercises versus usual care. For pain, function, and performance, all types of exercise were significantly better than usual care. The largest effect was observed for aerobic and mind-body exercises for function and pain. Strengthening and flexibility exercises had a moderate score, whereas mixed exercise gave the minimum score for all outcomes and was significantly less effective than aerobic or mind-body exercise for pain. The ranking mainly corresponded to the magnitude of the score shown by each exercise. Aerobic exercises were the best-ranked for performance and pain, whereas mind-body was also the best-ranked for self-reported pain and function. Strengthening and flexibility/skill generally received mid-level rankings while mixed exercises were the least ranked exercise [23].

It is confirmed that exercise is still important for people suffering from hip and knee OA for outcomes of performance function, pain. In addition, it was found that mind-body and aerobic exercise have the largest score for improvements in function and pain; strengthening and flexibility exercises improve multiple outcomes to a varying degree [23]. Older age is a well-known risk factor for OA; women are more likely to develop hand, foot, and knee OA compared to men [4].

Varus thrust increased the odds of worsening medial bone marrow lesions (BMLs) and medial cartilage loss as well as the odds of incident medial BMLs of the knee among those with KOA and those with increased risk of Knee OA according to the Multicenter Osteoarthritis Study (MOST) [24].

It was found that aerobic exercises have similar effects to mind-body exercises for controlling pain. Mind-body exercise such as yoga and tai chi can be characterized as mild to moderate intensity exercise performed with an intentional awareness (mindfulness) on breathing and slow controlled movement [25]. Although the underlying mechanism is not clear, the effect of both mind-body and aerobic exercises may be related to the possibility that these exercises affect the altered central nervous system such as central pain sensitization, mood disorders, and sleep disturbance. Pain experience is the result of interactions between these central failure and peripheral pain mechanisms, as aerobic and mind-body exercise can influence both central and peripheral pain mechanisms. There is no satisfactory explanation for the poor effect of mixed exercise, particularly when considering that there are many domains of physical impairment in people with OA [23].

So far, NSAIDs, symptomatic slow-acting drugs for OA, analgesics, bone-acting agents, putative disease-modifying agents, and agents for intra-articular injection including HA and corticosteroids have been used as pharmacological agents for treating OA. However, it has been reported that these agents are not efficient against the main cause of OA, may cause some side effects, and are not adequate for the long-term management of OA. NSAIDs are the most commonly used drugs for the management of OA. They showed moderate improvement against OA pain; however, it is advised that NSAIDs be used intermittently and not advised for longer periods. NSAIDs can be classified as cyclooxygenase-2 selective agents and nonselective agents [26].

## **2. Putative disease-modifying agents**

Putative disease-modifying drugs for OA like doxycycline, sprifermin, and cindunostat have not proved significant improvements of the joint so far although the clinical trials conducted to prove the effect of these drugs are still under trial [18].

## **3. Bone-acting agents**

Bone-forming agents or antiresorptive agents like zoledronic acid, risedronate, strontium ranelate, calcitonin, and vitamin D are classified as bone-acting agents for the management of OA. They are bone-acting agents that showed some recorded effect in the turnover of subchondral bone, although these agents did not show a significant improvement in the structure of the joint [26].

## **4. Agents for intra-articular injection**

Agents for intra-articular injection include HA and corticosteroids like triamcinolone, betamethasone, and methylprednisolone. Intra-articular injection of corticosteroids showed a greater beneficial effect. Furthermore, during follow-up periods of 3 and 6 months, intra-articular injection of HA showed a better therapeutic effect. Intra-articular injection of a combination of HA and corticosteroids showed a moderate beneficial effect on the pathological process of OA. However, for long-term pain control, intra-articular injection of HA did not show a significant improvement [26].

Use of nonpharmacological modalities (e.g. exercise) as a first-line management for knee OA is little to be compared with pharmacological modalities and usually associated with higher rates of surgical interventions. The results indicate that nonpharmacological agents such as exercise and weight reduction are effective in management of knee OA with minimal adverse side effects. Therefore, exercise and weight reduction should be advised as part of the treatment in most patients owing to their minimal side effects and cost effectiveness, as well as associated health benefits. It is important to specify resources and invest in supporting general practitioners and other primary health care providers to provide lifestyle interventions as a tool in managing knee OA [27].

Irrespective of a large body of evidence concerning the benefits of their use, opiates are used to manage pain associated with Knee OA. No studies fulfilled the inclusion criteria as the follow-up periods of these studies concerning safety were less than 6 months. A recent systematic review of chronic pain management found that there is insufficient evidence to support the effectiveness of long-term opioid therapy [28]. Opioids provide effective analgesia; however, benefits are usually encountered by frequent side effects such as nausea (30%), dizziness (20%), vomiting (13%), constipation (23%), and somnolence (18%) as well as the risk of addiction increases on chronic opioid use. The evidence on the safety and effectiveness of long-term opioid therapy for Knee OA cannot be evaluated. This is a concern and a limitation of the available evidence related to management of Knee OA. In the USA, there has been a significant increase in opioid prescriptions for patients suffering from knee OA, and opioids were prescribed to 15.9% of patients with knee OA [29].

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