Chapter 2: Osteoarthritis

INTRODUCTION

- *Osteoarthritis* (OA) is a common, progressive disorder affecting primarily weight-bearing diarthrodial joints, characterized by progressive destruction of articular cartilage, osteophyte formation, pain, limitation of motion, deformity, and disability.

PATHOPHYSIOLOGY

- *Primary* (*idiopathic*) *OA*, the more common type, has no known cause.
- *Secondary OA* is associated with a known cause such as inflammation, trauma, metabolic or endocrine disorders, and congenital factors.
- OA usually begins with damage to articular cartilage through injury, excessive joint loading from obesity or other reasons, or joint instability. Damage to cartilage increases activity of chondrocytes in attempt to repair damage, leading to increased synthesis of matrix constituents with cartilage swelling. Normal balance between cartilage breakdown and resynthesis is lost, with increasing destruction and cartilage loss.
- Subchondral bone adjacent to articular cartilage undergoes pathologic changes and releases vasoactive peptides and matrix metalloproteinases. Neovascularization and increased permeability of adjacent cartilage occur, which contribute to cartilage loss and chondrocyte apoptosis.
- Cartilage loss causes joint space narrowing and painful, deformed joints. Remaining cartilage softens and develops fibrillations, followed by further cartilage loss and exposure of underlying bone. New bone formations (osteophytes) at joint margins distant from cartilage destruction are thought to help stabilize affected joints.
- Inflammatory changes can occur in the joint capsule and synovium. Crystals or cartilage shards in synovial fluid may contribute to inflammation. Interleukin-1, prostaglandin E_2, tumor necrosis factor-α, and nitric oxide in synovial fluid may also play a role. Inflammatory changes result in synovial effusions and thickening.
- Pain may result from distention of the synovial capsule by increased joint fluid; microfracture; periosteal irritation; or damage to ligaments, synovium, or the meniscus.

CLINICAL PRESENTATION

- Risk factors include increasing age, obesity, sex, certain occupations and sports activities, history of joint injury or surgery, and genetic predisposition.
- The predominant symptom is deep, aching pain in affected joints. Pain accompanies joint activity and decreases with rest.
- Joints most commonly affected are the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hand, first carpometacarpal joint, knees, hips, cervical and lumbar spine, and first metatarsophalangeal (MTP) joint of the toe.
- Limitation of motion, stiffness, crepitus, and deformities may occur. Patients with lower extremity involvement may report weakness or instability.
- Upon arising, joint stiffness typically lasts less than 30 minutes and resolves with motion.
- Presence of warm, red, and tender joints suggests inflammatory synovitis.
- Physical examination of affected joints reveals tenderness, crepitus, and possibly enlargement. Heberden and Bouchard nodes are bony

enlargements (osteophytes) of the DIP and PIP joints, respectively.

DIAGNOSIS

- Diagnosis is made through patient history, physician examination, radiologic findings, and laboratory testing.
- American College of Rheumatology criteria for classification of OA of the hips, knees, and hands include presence of pain, bony changes on examination, normal erythrocyte sedimentation rate (ESR), and radiographs showing osteophytes or joint space narrowing.
- For hip OA, patients must have hip pain and two of the following: (1) ESR <20 mm/hr (5.6 µm/sec), (2) radiographic femoral or acetabular osteophytes, and/or (3) radiographic joint space narrowing.
- For knee OA, patients must have knee pain and radiographic osteophytes in addition to one or more of the following: (1) age >50 years, (2) morning stiffness lasting ≤30 minutes, (3) crepitus on motion, (4) bony enlargement, (5) bony tenderness, and/or (6) palpable joint warmth.
- ESR may be slightly elevated if inflammation is present. Rheumatoid factor is negative. Analysis of synovial fluid reveals high viscosity and mild leukocytosis (<2000 white blood cells/mm^3 [2×10^9/L]) with predominantly mononuclear cells.

TREATMENT

- Goals of Treatment: (1) Educate the patient, family members, and caregivers; (2) relieve pain and stiffness; (3) maintain or improve joint mobility; (4) limit functional impairment; and (5) maintain or improve quality of life.

Nonpharmacologic Therapy

- Educate the patient about the disease process and extent, prognosis, and treatment options. Promote dietary counseling, exercise, and a weight loss program for overweight patients.
- Physical therapy—with heat or cold treatments and an exercise program—helps maintain range of motion and reduce pain and need for analgesics.
- Assistive and orthotic devices (canes, walkers, braces, heel cups, and insoles) can be used during exercise or daily activities.
- Surgical procedures (eg, osteotomy, arthroplasty, joint fusion) are indicated for functional disability and/or severe pain unresponsive to conservative therapy.

Pharmacologic Therapy (Table 2-1)

TABLE 2-1

Medications for the Treatment of Osteoarthritis

Drug	Starting Dose	Usual Range
Oral analgesics		
Acetaminophen	325–500 mg three times a day	325–650 mg every 4–6 hours or 1 g three to four times/day
Tramadol	25 mg in the morning	Titrate dose in 25-mg increments to reach a maintenance dose of 50–100 mg three times a day
Tramadol ER	100 mg daily	Titrate to 200–300 mg daily
Hydrocodone/acetaminophen	5 mg/325 mg three	2.5–10 mg/325–650 mg three to five times daily

	times daily	
Oxycodone/acetaminophen	5 mg/325 mg three times daily	2.5–10 mg/325–650 mg three to five times daily
Topical analgesics		
Capsaicin 0.025%–0.15%		Apply to affected joint three to four times per day
Diclofenac 1% gel		Apply 2 or 4 g per site as prescribed, four times daily
Diclofenac 1.3% patch		Apply one patch twice daily to the site to be treated, as directed
Diclofenac 1.5% solution		Apply 40 drops to the affected knee, applying and rubbing in 10 drops at a time. Repeat for a total of four times daily.
Intra-articular corticosteroids		
Triamcinolone	5–15 mg per joint	10–40 mg per large joint (knee, hip, shoulder)
Methylprednisolone acetate	10–20 mg per joint	20–80 mg per large joint (knee, hip, shoulder)
NSAIDs		
Aspirin (plain, buffered, or enteric-coated)	325 mg three times a day	325–650 mg four times a day
Celecoxib	100 mg daily	100 mg twice daily or 200 mg daily
Diclofenac IR	50 mg twice a day	50–75 mg twice a day
Diclofenac XR	100 mg daily	100–200 mg daily
Diflunisal	250 mg twice a day	500–750 mg twice a day
Etodolac	300 mg twice a day	400–500 mg twice a day
Fenoprofen	400 mg three times a day	400–600 mg three to four times a day
Flurbiprofen	100 mg twice a day	200–300 mg/day in two to four divided doses
Ibuprofen	200 mg three times a day	1200–3200 mg/day in three to four divided doses
Indomethacin	25 mg twice a day	Titrate dose by 25–50 mg/day until pain controlled or maximum dose of 50 mg three times a day
Indomethacin SR	75 mg SR once daily	Can titrate to 75 mg SR twice daily if needed
Ketoprofen	50 mg three times a day	50–75 mg three to four times a day

Meclofenamate	50 mg three times a day	50–100 mg three to four times a day
Mefenamic acid	250 mg three times a day	250 mg four times a day
Meloxicam	7.5 mg daily	15 mg daily
Nabumetone	500 mg daily	500–1000 mg one to two times a day
Naproxen	250 mg twice a day	500 mg twice a day
Naproxen sodium	220 mg twice a day	220–550 mg twice a day
Naproxen sodium CR	750–1000 mg once daily	500–1500 mg once daily
Oxaprozin	600 mg daily	600–1200 mg daily
Piroxicam	10 mg daily	20 mg daily
Salsalate	500 mg twice a day	500–1000 mg two to three times a day

CR, controlled-release; ER, extended-release; IR, immediate-release; SR, sustained-release; XR, extended-release.

General Approach

- Drug therapy is targeted at relief of pain. A conservative approach is warranted because OA often occurs in older individuals with other medical conditions.
- Apply an individualized approach (**Figs. 2-1** and **2-2**). Continue appropriate nondrug therapies when initiating drug therapy.

FIGURE 2-1

Treatment recommendations for hip and knee osteoarthritis.

(CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.)

FIGURE 2-2

Treatment recommendations for hand osteoarthritis.

(CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.)

image

Knee and Hip OA

- **Acetaminophen** is a preferred first-line treatment; it may be less effective than oral nonsteroidal anti-inflammatory drugs (NSAIDs) but has a lower risk of serious gastrointestinal (GI) and cardiovascular (CV) events. Acetaminophen is usually well tolerated, but potentially fatal hepatotoxicity with overdose is well documented. It should be avoided in chronic alcohol users or patients with liver disease.

- **Nonselective NSAIDs** or **cyclooxygenase-2 (COX-2) selective inhibitors** (eg, **celecoxib**) are recommended if a patient fails acetaminophen. Nonselective NSAIDs may cause minor GI complaints such as nausea, dyspepsia, anorexia, abdominal pain, and diarrhea. They may cause gastric and duodenal ulcers and bleeding through direct (topical) or indirect (systemic) mechanisms. Risk factors for NSAID-associated ulcers and ulcer complications (perforation, gastric outlet obstruction, and GI bleeding) include longer duration of NSAID use, higher dosage, age older than 60 years, past history of peptic ulcer disease of any cause, history of alcohol use, and concomitant use of glucocorticoids or anticoagulants. Options for reducing the GI risk of nonselective NSAIDs include using (1) the lowest dose possible and only when needed, (2) misoprostol four times daily with the NSAID, and (3) a PPI or full-dose H_2-receptor antagonist daily with the NSAID.

- COX-2 inhibitors pose less risk for adverse GI events than nonselective NSAIDs, but this advantage is substantially reduced for patients taking aspirin. Both nonselective and selective NSAIDs are associated with an increased risk for CV events (hypertension, stroke, myocardial infarction, and death).

- NSAIDs may also cause kidney diseases, hepatitis, hypersensitivity reactions, rash, and CNS complaints of drowsiness, dizziness, headaches, depression, confusion, and tinnitus. NSAIDs inhibit COX-1–dependent thromboxane production in platelets, thereby increasing bleeding risk. Unlike aspirin, celecoxib and nonspecific NSAIDs inhibit thromboxane formation reversibly, with normalization of platelet function 1–3 days after drug discontinuation. Avoid NSAIDs in late pregnancy because of risk of premature closure of the ductus arteriosus. The most potentially serious drug interactions include use of NSAIDs with lithium, warfarin, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.

- **Topical NSAIDs** are recommended for knee OA if acetaminophen fails, and they are preferred over oral NSAIDs in patients older than 75 years. Topical NSAIDs provide similar pain relief with fewer adverse GI events than oral NSAIDs but may be associated with adverse events at the application site (eg, dry skin, pruritus, and rash). Patients using topical products should avoid oral NSAIDs to minimize the potential for additive side effects. Use of topical NSAIDs has not been linked with increased risk of CV events.

- **Intra-articular (IA) corticosteroid injections** are recommended for both hip and knee OA when analgesia with acetaminophen or NSAIDs is suboptimal. They can provide excellent pain relief, particularly when joint effusion is present. Local anesthetics such as lidocaine or bupivacaine are commonly combined with corticosteroids to provide rapid pain relief. Injections may also be given with concomitant oral analgesics for additional pain control. After aseptic aspiration of the effusion and corticosteroid injection, initial pain relief may occur within 24–72 hours, with peak relief occurring after 7–10 days and lasting for 4–8 weeks. Local adverse effects can include infection, osteonecrosis, tendon rupture, and skin atrophy at the injection site. Do not administer injections more frequently than once every 3 months to minimize systemic adverse effects. Systemic corticosteroid therapy is not recommended in OA, given lack of proven benefit and well-known adverse effects with long-term use.

- **Tramadol** is recommended for hip and knee OA in patients who have failed scheduled full-dose acetaminophen and topical NSAIDs, who are not appropriate candidates for oral NSAIDs, and who are not able to receive IA corticosteroids. Tramadol can be added to partially effective acetaminophen or oral NSAID therapy. Tramadol is associated with opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence. However, tramadol is not associated with life-threatening GI bleeding, CV events, or renal failure. The most serious adverse event is seizures. Tramadol is classified as a Schedule IV controlled substance due to its potential for dependence, addiction, and diversion. There is increased risk of serotonin syndrome when tramadol is used with other serotonergic medications, including duloxetine.

- **Opioids** should be considered in patients not responding adequately to nonpharmacologic and first-line pharmacologic therapies. Patients who are at high surgical risk and cannot undergo joint arthroplasty are also candidates for opioid therapy. Use opioid analgesics in the lowest effective dose and the smallest quantity needed. Avoid combinations of opioids and sedating medications whenever possible. Inform patients on how to use, store, and dispose of opioid medications. Sustained-release compounds usually offer better pain control throughout the day. Common adverse effects include nausea, somnolence, constipation, dry mouth, and dizziness. Opioid dependence, addiction, tolerance, hyperalgesia, and issues surrounding drug diversion may be associated with long-term treatment. Assess opioid use at least every 3 months, evaluating patient progression toward functional treatment goals, risks of harm, and adverse effects.

- **Duloxetine** can be used as adjunctive treatment of knee (not hip) OA in patients with partial response to first-line analgesics (acetaminophen, oral NSAIDs). It may be a preferred second-line medication in patients with both neuropathic and musculoskeletal OA pain. Pain reduction occurs after about 4 weeks of therapy. Duloxetine may cause nausea, dry mouth, constipation, anorexia, fatigue, somnolence, and dizziness. Serious rare events include Stevens-Johnson syndrome and liver failure. Concomitant use with other medications that increase serotonin concentration (including

tramadol) increases risk of serotonin syndrome.

- **IA hyaluronic acid** (sodium hyaluronate) is not routinely recommended because injections have shown limited benefit for knee OA and have not been shown to benefit hip OA. Injections are usually well tolerated, but acute joint swelling, effusion, stiffness, and local skin reactions (eg, rash, ecchymoses, or pruritus) have been reported. IA preparations and regimens for OA knee pain include:

  - ✔ **Cross-linked hyaluronate 30 mg/3 mL** (Gel-One) single injection
  - ✔ **Hyaluronan 30 mg/2 mL** (Orthovisc) once weekly for three injections
  - ✔ **Hyaluronan 88 mg/4 mL** (Monovisc) single injection
  - ✔ **Hylan polymers 16 mg/2 mL** (Synvisc) once weekly for three injections
  - ✔ **Hylan polymers 48 mg/6 mL** (Synvisc-One) single injection
  - ✔ **Sodium hyaluronate 20 mg/2 mL** (Hyalgan) once weekly for five injections
  - ✔ **Sodium hyaluronate 20 mg/2 mL** (Euflexxa) once weekly for three injections
  - ✔ **Sodium hyaluronate 25 mg/2.5 mL** (Supartz FX) once weekly for five injections
  - ✔ **Sodium hyaluronate 25 mg/2.5 mL** (GenVisc 850) once weekly for five injections

- **Glucosamine and/or chondroitin** and **topical rubefacients** (eg, **methyl salicylate, trolamine salicylate**) lack uniform improvement in pain control or functional status for hip and knee pain and are not preferred treatment options. Glucosamine adverse effects are mild and include flatulence, bloating, and abdominal cramps. The most common adverse effect of chondroitin is nausea.

Hand OA

- **Topical NSAIDs** are a first-line option for hand OA. Topical diclofenac has efficacy similar to oral NSAIDs with fewer adverse GI events, albeit with some local application site events. Efficacy with topical NSAIDs typically occurs with 1–2 weeks.
- **Oral NSAIDs** are an alternative first-line treatment for patients who cannot tolerate the local skin reactions or who received inadequate relief from topical NSAIDs.
- **Capsaicin cream** is an alternative first-line treatment; small clinical trials have demonstrated about 50% reduction in pain scores. It is a reasonable option for patients unable to take oral NSAIDs. Capsaicin must be used regularly to be effective, and it may require up to 2 weeks to take effect. Adverse effects are primarily local and include burning, stinging, and/or erythema that usually subsides with repeated application. Warn patients not to get cream in their eyes or mouth and to wash hands after application. Application of the cream, gel, solution, or lotion is recommended four times daily.
- **Tramadol** is an alternative first-line treatment and is a reasonable option for patients who do not respond to topical therapy and are not candidates for oral NSAIDs because of high GI, CV, or renal risks. Tramadol may also be used in combination with partially effective acetaminophen, topical therapy, or oral NSAIDs.

EVALUATION OF THERAPEUTIC OUTCOMES

- To monitor efficacy, assess baseline pain with a visual analog scale, and assess range of motion for affected joints with flexion, extension, abduction, or adduction.
- Depending on the joint(s) affected, measurement of grip strength and 50-ft walking time can help assess hand and hip/knee OA, respectively.
- Baseline radiographs can document extent of joint involvement and follow disease progression with therapy.
- Other measures include the clinician's global assessment based on patient's history of activities and limitations caused by OA, the Western Ontario

and McMaster Universities Arthrosis Index, Stanford Health Assessment Questionnaire, and documentation of analgesic or NSAID use.

- Ask patients about adverse effects from medications. Monitor for signs of drug-related effects, such as skin rash, headaches, drowsiness, weight gain, or hypertension from NSAIDs.
- Obtain baseline serum creatinine, hematology profile, and serum transaminases with repeat levels at 6- to 12-month intervals to identify specific toxicities to the kidney, liver, GI tract, or bone marrow.

See Chapter 106, Osteoarthritis, authored by Lucinda M. Buys and Sara A. Wiedenfeld, for a more detailed discussion of this topic.