

CLINICAL PRACTICE

Osteoarthritis of the Knee

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 66-year-old woman who is overweight reports bilateral knee pain of gradual onset during the past several months that increasingly has limited her activities. Last week, when walking down the stairs, she nearly fell when her knee gave way. She does not recall having injured her knee, and she has no morning stiffness and no pain in other joints. She has tried taking up to eight extra-strength (500 mg each) acetaminophen tablets daily without success and has never had ulcers or stomach bleeding. How should the patient be evaluated and treated?

THE CLINICAL PROBLEM

Approximately 25 percent of persons 55 years of age or older have had knee pain on most days in a month in the past year,¹ and about half of them have radiographic osteoarthritis in the knee, a group considered to have symptomatic osteoarthritis. Many without radiographic osteoarthritis of the knee probably have osteoarthritis that is not yet visible on radiography, an imaging procedure insensitive to early disease.

Osteoarthritis of the knee increases in prevalence with age and is more common in women than in men. Risk factors include obesity, knee injury, previous knee surgery, and occupational bending and lifting.² Osteoarthritis of the knee can be part of a generalized diathesis, including osteoarthritis of the hand, which may be inherited. The natural history of osteoarthritis of the knee is highly variable, with the disease improving in some patients, remaining stable in others, and gradually worsening in others. Osteoarthritis is a leading cause of impaired mobility in the elderly.³ Many persons with knee pain have limitations in function that prevent them from engaging in their usual activities.

Osteoarthritis affects all structures within a joint. Not only is hyaline articular cartilage lost, but bony remodeling occurs, with capsular stretching and weakness of periarticular muscles. In some patients, synovitis is present, laxity of the ligaments occurs, and lesions in the bone marrow develop that may represent trauma to bone.⁴ Osteoarthritis involves the joint in a nonuniform and focal manner. Localized areas of loss of cartilage can increase focal stress across the joint, leading to further cartilage loss. With a large enough area of cartilage loss or with bony remodeling, the joint becomes tilted, and malalignment develops. Malalignment is the most potent risk factor for structural deterioration of the joint,⁵ since it increases further the degree of focal loading, creating a vicious cycle of joint damage that ultimately can lead to joint failure. Local inflammation in the synovium and the cartilage may contribute to pain and joint damage.⁶

The following three joint compartments combine to form the knee: the lateral tibiofemoral compartment, the medial tibiofemoral compartment, and the patellofemoral compartment. Although any of these three compartments may be a source

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of the pain associated with osteoarthritis, pain emanates most often from the patellofemoral joint.⁷ Bone,⁸ synovial inflammation, and a stretched joint capsule filled with fluid⁹ are likely to be sources of pain; bursitis can also cause symptoms.¹⁰ Hyaline articular cartilage is unlikely to be a source of pain, since it contains no nociceptive fibers.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The pain of osteoarthritis is usually related to activity. For osteoarthritis of the knee (Fig. 1), activities such as climbing stairs, getting out of a chair, and walking long distances bring on pain. Morning stiffness usually lasts less than 30 minutes.¹¹ Patients often note that their knees “give way,” a so-called instability symptom.

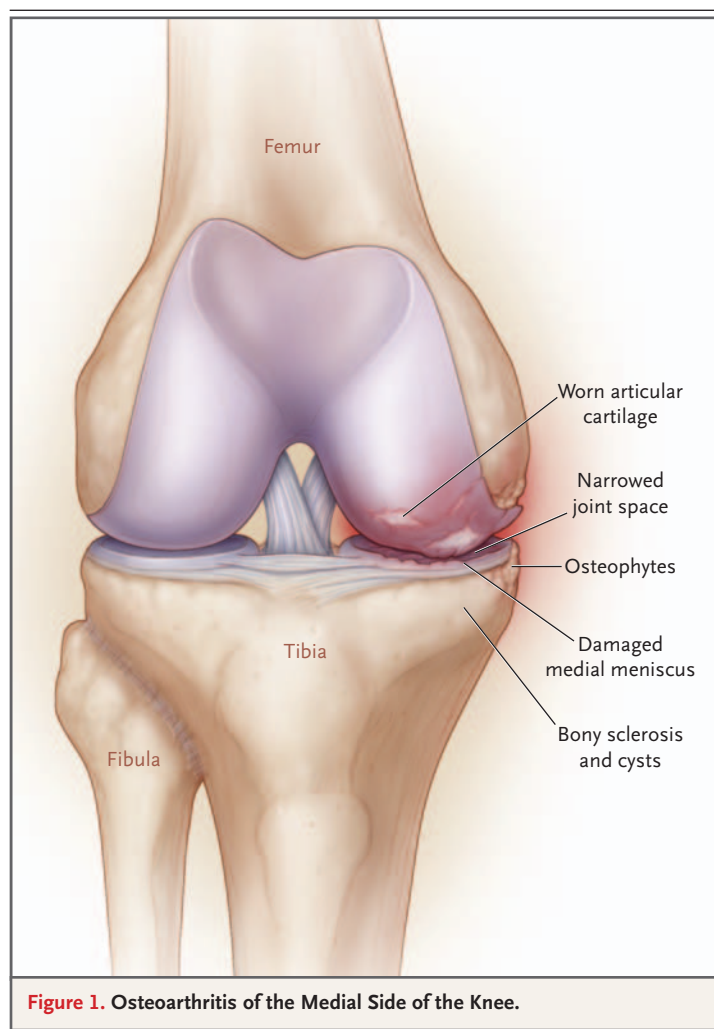


Figure 1. Osteoarthritis of the Medial Side of the Knee.

Since the knee does not bend much during walking on level ground, the patella does not articulate with the underlying femur, and pain during this activity is not likely to originate in the patellofemoral joint. With more knee bending, such as that which occurs during sitting, stair climbing, or jumping, the patella articulates with the femoral trochlea, and pain during these activities is typical of that originating in the patellofemoral joint. A history of the knee giving way may indicate the presence of an internal derangement such as a meniscal tear or a tear of the anterior cruciate ligament. However, it may also reflect weakness of the muscles that support the joint. Pain in the knee at night reflects either severe symptomatic disease or pain from causes other than osteoarthritis, such as inflammatory arthritis, tumors, infection, or crystal disease (Table 1).

Examination of the patient should include testing for various possible causes of knee pain (Table 1). Since arthritis of the hip can cause referred pain to the knee, range of motion of the hip should be assessed to see whether movement at the hip joint induces knee pain or whether there is groin tenderness. Bursitis (either anserine or trochanteric) should also be ruled out. Trochanteric bursitis is part of a syndrome of lateral hip and thigh pain that can extend distally to the tensor fascia lata and even to the iliotibial band, causing lateral knee pain that occurs especially with bending of the knee. Examination of the iliotibial band and more proximal structures in the lateral thigh can identify the source of pain (Table 1). Both anserine and trochanteric bursitis can be treated effectively with a local injection of a corticosteroid.

Tenderness at the junction of the femur and tibia (the joint line) should be evaluated, as should the presence of an effusion. Examination of the patient should include an evaluation of whether the legs are varus (bowlegged) or valgus (knock-kneed), a physical finding that usually signifies marked malalignment. The knees are farther apart than the feet in the frontal plane when a person with varus malalignment is standing, and the knees are closer together than the feet in a person with valgus malalignment. Varus and valgus malalignment are strong risk factors for worsening radiographic disease^{4,5} and are probably associated with functional limitations.⁵ In addition, gait should be observed to determine wheth-

Table 1. Features That Distinguish Various Causes of Chronic Knee Pain from Osteoarthritis.*

| Condition | Features According to History | Features of Physical Examination | Laboratory Features |
|--|--|---|---|
| Chronic inflammatory arthritis, including rheumatoid arthritis | Prominent morning stiffness Other joints affected | Other joints swollen or tender | Increased erythrocyte sedimentation rate Inflammatory synovial fluid |
| Gout or pseudogout | Other joints affected (especially in cases of gout) | Other joints swollen or tender | Inflammatory synovial fluid containing crystals |
| Hip arthritis | | Pain with hip rotation Groin tenderness | |
| Chondromalacia patellae | Relatively young age of the patient Predominance of patellofemoral symptoms | Tenderness only over the patellofemoral joint | |
| Anserine bursitis | | Tenderness distal to the knee over the medial tibia | |
| Trochanteric bursitis | Lateral hip pain | Tenderness in the region of the lateral hip | |
| Iliotibial band syndrome | | Tenderness of the iliotibial band† | |
| Joint tumors | Nocturnal or continuous pain | | Bloody synovial fluid Possibility of an abnormal radiograph |
| Meniscal tear | Prominent mechanical symptoms (e.g., buckling or locking) | Tenderness over the joint line Positive McMurray test‡ | Meniscal tear on MRI |
| Anterior cruciate ligament tear | Prominent mechanical symptoms | Positive Lachman test§ | Anterior cruciate ligament tear on MRI |

* Knee pain is defined as chronic if it is present for at least six weeks. MRI denotes magnetic resonance imaging.

† Tenderness of the iliotibial band is usually lateral to the knee over the insertion site of the iliotibial band in the fibular head or superior to that, where it courses over the lateral femoral condyle.

‡ No physical examination maneuver for meniscal tears has both high sensitivity and specificity.¹² Tenderness at the joint line has a sensitivity of 79 percent and a specificity of 15 percent, whereas a McMurray test has a sensitivity of 53 percent and a specificity of 59 percent. A McMurray test is positive if a click is palpable over the medial or lateral tibiofemoral joint line during flexion and extension of the knee during varus (medial tear) or valgus (lateral tear) stress. These data are derived from studies of acute tears,¹² and diagnostic data are not available for chronic tears.

§ A Lachman test is positive if there is excessive anterior translation of the tibia at 30 degrees of knee flexion.

er there is antalgia (a limp secondary to pain) and whether gait has slowed because of knee pain. If the patient uses a cane, appropriate use of the cane should be assessed during gait.

The location of tenderness in the knee is sometimes helpful in diagnosis, although its reproducibility is limited.¹³ Tenderness over the medial or lateral joint lines often signals disease there but is also common with meniscal tears.¹² Patellofemoral tenderness provides evidence of involvement of the patellofemoral compartment with either osteoarthritis, inflammatory arthritis, or other conditions (Table 1). Tears of the anterior cruciate ligament, if acute, may cause pain. The anterior cruciate ligament prevents translation of the tibia anteriorly during flexion of the knee, and when there is anterior cruciate ligament insufficiency, a Lachman test is more often positive than is an anterior drawer test (Table 1).¹² In patients with advanced osteoarthritis, meniscal tears are nearly universal¹⁴ and anterior cruciate

ligament tears are common¹⁵; diagnosing them is not likely to change treatment. Repairing meniscal tears in patients with osteoarthritis is unlikely to improve the disease course or ameliorate pain; meniscal tears are not associated with pain in osteoarthritis.^{14,16}

LABORATORY TESTS

No blood tests are routinely indicated in the workup of a patient with chronic knee pain unless symptoms and signs suggest rheumatoid arthritis or other forms of inflammatory arthritis (Table 1). Examination of synovial fluid is indicated if inflammatory arthritis or gout or pseudogout is suspected or if joint infection is a concern; a white-cell count below 1000 per cubic millimeter in the synovial fluid is consistent with osteoarthritis, whereas higher white-cell counts suggest inflammatory arthritis. The presence of crystals is diagnostic of either gout or pseudogout.

Radiography is indicated in the workup of a

patient if knee pain is nocturnal or is not activity-related. If knee pain persists after effective therapy for osteoarthritis, a radiograph may reveal clues to a missed diagnosis. In patients with osteoarthritis, the radiographic findings correlate poorly with the severity of pain (Fig. 2), and radiographs may be normal in persons with disease.¹⁷ Although chondrocalcinosis may be seen on the radiograph, it is an age-related finding that is inconsistently associated with knee pain.¹⁸ Avascular necrosis can be diagnosed with radiography, although if it is seen, it is often too late to treat it. Magnetic resonance imaging (MRI) is likely to reveal changes that indicate the presence of osteoarthritis, but it is not suggested in the workup of older persons with chronic knee pain. MRI findings of osteoarthritis, including meniscal tears, are common in middle-aged and older adults¹⁴ with and without knee pain.

TREATMENT

Treatment of osteoarthritis involves alleviating pain, attempting to rectify mechanical malalignment, and identifying and addressing manifestations of joint instability.

Nonsteroidal Antiinflammatory Drugs, Cyclooxygenase-2 Inhibitors, and Acetaminophen

For treating the pain of osteoarthritis of the knee, head-to-head randomized trials showed that nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors are more efficacious than acetaminophen.^{19,20} However, the superiority of NSAIDs over acetaminophen (at doses of 4 g per day) is modest.²⁰ In one large crossover trial,¹⁹ the average reduction in pain during the first treatment period, on a scale of 0 to 100, was 21 in patients treated with NSAIDs and 13 in those given acetaminophen ($P < 0.001$). Because of the greater toxicity of NSAIDs, acetaminophen should be the first line of therapy. Acetaminophen appears less effective, however, among patients who have already received treatment with NSAIDs; in the crossover trial there was no improvement overall with acetaminophen in patients treated after a six-week course of NSAIDs.¹⁹ Low doses of antiinflammatory medications (e.g., 1200 mg of ibuprofen per day)²¹ are less efficacious but better tolerated than high doses (e.g., 2400 mg of ibuprofen per day).²² One strategy to decrease the potential gastric toxic-



Figure 2. Radiograph Showing Osteoarthritis of the Medial Side of the Knee.

Narrowing of the medial joint space (arrow) and osteophytes (arrowhead) are shown.

ity of conventional NSAIDs has been the use of COX-2 inhibitors,²³ although the results of recent trials showing increased cardiovascular risk with these agents has limited their use.²⁴ Alternatively, the combination of NSAIDs and misoprostol or proton-pump inhibitors has been shown in randomized trials to reduce the number of endoscopically confirmed ulcers associated with NSAIDs (Table 2).

Injections of Hyaluronic Acid

Injections of hyaluronic acid into the knee joint have been approved by the Food and Drug Administration for the treatment of osteoarthritis. However, data on efficacy are inconsistent. Two recent meta-analyses^{27,28} reported statistically significant but limited efficacy. In one meta-analysis, publication bias (preferential publication of positive studies) was seen, which can inflate meta-analysis estimates from published studies. The identification of two large, unpublished trials whose data showed no efficacy,²⁸ and the observation that injections of hyaluronic acid appeared to be less effective in large than in small trials, suggest that even limited efficacy may be an overestimate.

Glucosamine and Chondroitin Sulfate

Glucosamine and chondroitin sulfate are widely used for the treatment of osteoarthritis, although their mechanisms of action are unclear. Most randomized controlled trials have reported greater pain relief with treatment with either compound than with placebo²⁸ and have found little toxicity, usually no more than that associated with place-

Table 2. Pharmacologic Treatment for Osteoarthritis of the Knee.

| Treatment | Dosage | Comments |
|-----------------------------|--|---|
| Acetaminophen | Up to 1 g 4 times a day | Patients with liver disease or alcoholism should avoid. Prolongs half-life of warfarin. |
| NSAIDs* | | |
| Naproxen | 375–500 mg twice a day | Take with food. High rates of gastrointestinal side effects, including ulcers and bleeding, occur. Patients at high risk for gastrointestinal side effects should also take either a proton-pump inhibitor or misoprostol.† There is an increased concern about side effects (gastrointestinal or bleeding) when taken with acetylsalicylic acid. Can also cause edema and renal insufficiency. |
| Salsalate | 1500 mg twice a day | |
| Ibuprofen | 600–800 mg 3 to 4 times a day | |
| Cyclooxygenase-2 inhibitors | | |
| Celecoxib | 100–200 mg per day | High doses are associated with an increased risk of myocardial infarction and stroke. Can cause edema and renal insufficiency. |
| Glucosamine | 1500 mg per day | Side effects are similar to those with placebo. |
| Chondroitin | 1200 mg per day | Side effects are similar to those with placebo. |
| Opiates | Various | Common side effects include dizziness, sedation, nausea or vomiting, dry mouth, constipation, urinary retention, and pruritus. Respiratory and central nervous system depression can occur. |
| Capsaicin | 0.025–0.075% cream 3 to 4 times a day | Can irritate mucous membranes. |
| Intraarticular injections | | |
| Hyaluronic acid | Varies from 3 to 5 weekly injections, depending on preparation | Mild to moderate pain at injection site. |
| Steroids | | |

* NSAIDs denotes nonsteroidal antiinflammatory drugs.

† Patients at high risk include those with previous gastrointestinal events, persons 60 years of age or older, and persons taking corticosteroids.²⁵ Trials have shown the efficacy of proton-pump inhibitors and misoprostol in the prevention of ulcers and bleeding.²⁶ Misoprostol is associated with a high rate of diarrhea and cramping; therefore, proton-pump inhibitors are more widely used to reduce NSAID-related gastrointestinal symptoms.

bo. Publication bias was found as part of a meta-analysis of published trials evaluating these treatments, and this suggests that efficacy results from only published reports may be inflated.^{28,29} Four trials published since this meta-analysis, including two that were large enough to detect modest treatment effects, have shown no efficacy of glucosamine.^{30,31} Results of a recently completed multicenter trial of glucosamine and chondroitin, which was funded by the National Institutes of Health, appear in this issue of the *Journal*.³²

Other Pharmacologic Therapies

In randomized trials, intraarticular corticosteroid injections have relieved pain more effectively than placebo for one to three weeks on average, after which their comparative efficacy wanes.³³ Data

are lacking about the optimal number or frequency of corticosteroid injections. Opiate analgesic agents are more efficacious than placebo in controlling pain, but side effects and dependence are concerns. Topical compounds such as capsaicin have been modestly better than placebo in reducing the pain of osteoarthritis of the knee (Table 2).³⁴

Nonpharmacologic Treatment

Too little attention is paid to nonpharmacologic treatments (Table 3). In patients with osteoarthritis of the knee, weakness of the quadriceps muscles is caused by disuse and by inhibition of muscle contraction in the presence of adjacent capsular swelling (so-called arthrogenous muscle inhibition).³⁵ The severity of pain is directly correlated with the degree of muscle weakness.³⁶

Table 3. Nonpharmacologic Treatment for Osteoarthritis of the Knee.

| Treatment | Comments |
|----------------------------|---|
| Exercise | |
| Resistance training | Avoid if joint pain worsens. Progressive training is most effective. Exercises in a pool or partial-weight-bearing exercises are often tolerated better than equivalent full-weight-bearing exercises. |
| Aerobic | |
| Unloading | |
| Cane or crutch | A cane should be held contralateral to the affected knee with the hand at the level of the greater trochanter of the hip. The cane and the affected leg should contact the ground at the same time. |
| Weight loss | |
| Realignment | |
| Braces and patellar taping | Indicated when malalignment is noted on examination and pain is unresponsive to other medical treatments. Braces or taping can cause skin irritation and can impede the return of blood flow from the distal leg. |
| Shoe inserts | |
| Acupuncture | Reduces pain on average only moderately after several sessions. |

Although strong muscles may promote structural deterioration in malaligned knees,³⁷ strengthening the muscles is still important because stronger muscles improve the stability of the joints and lessen pain.

Exercises are likely to be most effective if they train muscles for the activities a person performs daily. Range-of-motion exercises, which do not strengthen muscles, and isometric exercises, which strengthen muscles, but not through a range of motion, are unlikely to be effective. To reduce pain and improve function, randomized trials have demonstrated the efficacy of isokinetic or isotonic strengthening (i.e., strengthening that occurs when a person flexes or extends the knee against resistance).^{38,39} Low-impact aerobic exercise is also effective³⁸ in lessening pain. Exercise regimens may differ for persons with patellofemoral symptoms. If the knee hurts during an exercise, then that exercise should be avoided. The involvement of a physical therapist is often warranted.

In a recent randomized trial, the combination of exercise and modest weight loss (mean, 4.6 kg) — but not weight loss alone — reduced pain and improved physical function in patients with osteoarthritis of the knee as compared with education about nutrition, exercise, and arthritis.⁴⁰ In a large controlled trial, acupuncture was shown to reduce pain in patients with osteoarthritis of the knee,⁴¹ as compared with no acupuncture and sham acupuncture, but the effect was small.

Correction of Malalignment

Malalignment is induced over a long period by anatomic alterations of the joint and bone, and correcting it is challenging. Evidence from randomized trials is sparse regarding the efficacy of therapies to correct malalignment across the knee joint. In one trial of patients with osteoarthritis of the medial side of the knee and varus malalignment, wearing a neoprene sleeve over the knee decreased knee pain moderately and significantly as compared with no treatment⁴²; the use of a valgus brace (which also can lessen varus malalignment)⁴¹ decreased pain significantly more than the sleeve.⁴²

Other ways of correcting malalignment across the knee include the use of wedged insoles or orthotics in footwear. In patients with osteoarthritis and varus malalignment of the knees, a shoe wedge (thicker laterally) moves the center of loading laterally during walking, a change that extends from foot to knee, lessening medial load across the knee. Although such modifications to footwear decrease varus malalignment,⁴³ one randomized trial⁴⁴ showed no reduction in pain as compared with a neutral insert.

Patellofemoral pain may be caused by tilting or malalignment of the patella. Patellar realignment with the use of braces or tape to pull the patella back into the trochlear sulcus of the femur or reduce its tilt may lessen pain. In clinical trials in which tape was used to reposition the patella into the sulcus without tilt, knee pain was reduced as compared with placebo.^{45,46} However, patients may find it difficult to apply tape, and skin irritation is common. Commercial patellar braces are also available, but their efficacy has not been studied formally.

GUIDELINES

Guidelines are available for the treatment of knee osteoarthritis⁴⁷⁻⁴⁹ but predate the publication of many of the trials of interventions discussed in this review.

SUMMARY AND RECOMMENDATIONS

Knee pain related to activity, such as in the woman in the vignette, is characteristic of osteoarthritis. Physical examination should be performed to rule out findings suggestive of other causes of knee pain and to assess for abnormalities associated with osteoarthritis, such as varus or valgus de-

formity. Radiographs of the knee are not indicated routinely, although I would order these in the case described in the vignette, given the lack of response to acetaminophen. If there is an effusion, arthrocentesis should be considered.

On the basis of data from randomized trials and the lack of efficacy of acetaminophen, I would treat the patient with an NSAID as needed (with food), and given her age, I would add a proton-pump inhibitor. Topical capsaicin has been shown to be of moderate benefit in reducing pain and could also be considered. An intraarticular corticosteroid injection could alleviate pain for the short term.

I would refer the patient to physical therapy for exercises to strengthen the quadriceps and for an evaluation of function, and I would re-

inforce the importance of exercise by asking the patient to demonstrate her exercises and report how often she does them. Weight loss should be recommended along with exercise.

Although data are limited to support the use of a neoprene sleeve, I would recommend that the patient use one when she walks, even in the absence of varus deformity, because of her symptoms of pain and because her knee gives way. Should the sleeve be ineffective, I would fit her for a valgus knee brace if she would be willing to wear one and if she has a varus deformity.

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CORRECTION

Osteoarthritis of the Knee

Osteoarthritis of the Knee . On page 844, the arrowhead in Figure 2 was misplaced. A corrected version of the figure is available with the full text of the article at www.nejm.org.