X OSTEOARTHRITIS

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Definition

Osteoarthritis is a common form of arthritis characterized by degeneration of articular cartilage and pathologic changes in surrounding bone and periarticular tissue. The disease process results in pain and dysfunction of affected joints and is a major cause of disability in the general population. Osteoarthritis is also frequently referred to as degenerative joint disease; other terms that have been used include osteoarthrosis, hypertrophic arthritis, and atrophic arthritis.

Classification

PRIMARY OSTEOARTHRITIS

Patients without a specific inflammatory or metabolic condition known to be associated with arthritis and who do not have a history of specific injury or trauma are considered to have primary osteoarthritis. However, a number of underlying processes are considered to be important in patients with primary osteoarthritis [see Etiologic Factors, Risk Factors, below]. In most patients, involvement is limited to one or a small number of joints or joint areas. In some patients, however, multiple joint areas are involved; these patients are considered to have a separate variant called primary generalized osteoarthritis. Another variant, termed erosive osteoarthritis, is characterized by polyarticular involvement of the small joints of the hand and tends to occur more often in middle-aged and elderly women.

SECONDARY OSTEOARTHRITIS

Secondary osteoarthritis has been associated with several conditions that cause damage to articular cartilage through a variety of mechanisms, including mechanical, inflammatory, and metabolic processes [see Table 1]. Acute trauma, particularly intra-articular fractures and meniscal tears, can result in articular instability or incongruity and can lead to osteoarthritis years after an injury.

The role of chronic trauma from certain occupational or avocational activities is not as well established as the role of acute trauma in the development of secondary osteoarthritis. Neuropathic arthropathy (Charcot joint) is characterized by polyarticular involvement of the small joints of the hand and tends to occur more often in middle-aged and elderly women.

Table 1 Causes of Secondary Osteoarthritis

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Trauma</td>
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<td>Acute injury</td>
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<td>Chronic occupational overuse</td>
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<td>Sports overuse</td>
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<td>Neuropathic arthropathy (Charcot joint)</td>
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<td>Inflammatory arthritis</td>
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<td>Rheumatoid arthritis</td>
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<td>Infectious arthritis</td>
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<td>Psoriatic arthritis</td>
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<td>Reactive arthritis</td>
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<td>Ankylosing spondylitis</td>
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<td>Dysplastic and hereditary conditions</td>
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<td>Congenital hip dysplasia</td>
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<td>Epiphyseal dysplasia</td>
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<td>Chondroplasias</td>
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<td>Perthes disease</td>
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<td>Kashin-Bek disease</td>
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<td>Joint hypermobility</td>
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<td>Bone disorders</td>
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<td>Osteonecrosis (avascular necrosis)</td>
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<td>Osteochondritis</td>
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<td>Paget disease of bone</td>
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<td>Metabolic and endocrine disorders</td>
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<td>Crystal deposition disease (gout, calcium pyrophosphate deposition, basic calcium phosphate)</td>
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<td>Hemochromatosis</td>
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<td>Ochronosis</td>
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<td>Wilson disease</td>
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<td>Bleeding disorders</td>
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<td>Acromegaly</td>
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Primary bone disorders that affect the mechanics and articular surfaces of nearby joints may also lead to degenerative cartilage changes, particularly around major joints such as the shoulder, hip, and knee. Several metabolic and endocrine disorders have been associated directly or indirectly with the development of osteoarthritis, often with atypical patterns or in unusual locations. In most of these conditions, cartilage damage is associated with the accumulation, in articular cartilage, of a particular substance associated with the metabolic condition (e.g., uric acid or iron). In hemochromatosis, the mechanism of joint damage may also be associated with calcium pyrophosphate crystal deposition. In acromegaly, overgrowth of articular cartilage and subsequent mechanical problems appear to be important in the pathogenesis of the disease.

Epidemiology

Osteoarthritis is the most common type of arthritis, and it is one of the most common causes of disability and dependence in the United States. Estimating the prevalence of osteoarthritis in the general population is difficult because of the high prevalence of asymptomatic radiographic changes of osteoarthritis and differences in case definition. The prevalence of radiographic changes of osteoarthritis in the population in general, regardless of symptoms, is roughly 30% for the hands, 21% for the feet, and...
3% for the knees and hips. In persons older than 65 years, changes are seen in the knee in 33% and in the hands in almost 100%. Fortunately, most patients with radiographic changes found in population-based surveys have few symptoms or functional limitations. Men and women 30 to 60 years of age have equal overall prevalence of symptomatic osteoarthritis (approximately 6% have affected knees and 4% have affected hips). For adults older than 60 years, however, the prevalence of symptomatic osteoarthritis (all joints) increases to 17% in men and 30% in women.1,2

Men and women tend to be affected equally by osteoarthritis in middle age, but after 50 years of age, women are affected more often, particularly in the interphalangeal joints of the fingers.3 Osteoarthritis is seen in all population groups, although prevalence can vary with certain geographic areas and ethnic groups. For example, osteoarthritis of the hip is least common in Japanese, Saudi Arabian, Chinese, and African populations; and knee involvement is most common in African-American women. Comparisons of osteoarthritis prevalence have shown that hip involvement is less common, but knee involvement is more common, in Chinese men and women than in white men and women in the United States.4-6

Etiologic Factors

RISK FACTORS

A number of risk factors are believed to contribute to the development of primary osteoarthritis, including age, obesity, joint malalignment, bone density, hormonal status, nutritional factors, joint dysplasia, trauma, occupational factors, and hereditary factors.3

Age is the factor most strongly associated with radiographic and clinically significant osteoarthritis, with an exponential increase seen in more severely involved joints. The cellular or biomechanical changes in articular cartilage that occur with aging are not necessarily those seen in osteoarthritis. However, it has been speculated that these changes may facilitate the development of disease.

Obesity is clearly associated with osteoarthritis of the knee. The increased load carried by obese persons and the alterations in gait and posture that redistribute this load, as well as the deleterious effects of lepton on articular cartilage, may contribute to structural damage to articular cartilage.4 A study in young men suggested that each increase in weight of 8 kg results in a 70% increase in the risk of symptomatic arthritis of the knee in later years.5 This association is particularly high in patients with varus malalignment of the knee, and obese patients with malalignment are at risk for more rapid progression of established osteoarthritis in the knee.6,9 Most of the association of obesity with osteoarthritis of the knee appears to be related to environmental, rather than genetic, factors.1 The relation of obesity to osteoarthritis in other weight-bearing joints is not as clear-cut and may not be much of a factor at all for hip involvement.

An association between increased bone density and osteoarthritis has been noted in several studies.10-12 Women with osteoporosis and hip fractures have a decreased risk of osteoarthritis, and those affected by osteoarthritis have significantly increased bone density. This negative association suggests that soft subchondral bone absorbs impact and protects articular cartilage better than dense bone. Paradoxically, however, observations regarding the quality of subchondral bone, estrogen deficiency, and dietary vitamin D intake suggest that strong subchondral bone may be particularly important in preventing progression of osteoarthritis once it is established.13,14 Chronic repetitive impact loading is known to cause rapid degenerative changes in articular cartilage in laboratory animals. This mechanism probably accounts for the high frequency of osteoarthritis in certain occupational and athletic settings. In particular, occupational activities that require frequent knee bending increase the risk of knee involvement, and frequent lifting appears to be a risk factor for hip involvement.15-17 Long-term weight-bearing sports activity is associated with an increased risk of developing radiographic evidence of osteoarthritis. In patients without a history of injury, clinical symptoms do not always correlate well with radiographic changes, and radiographic changes do not often progress significantly, even in older long-distance runners.18,19 However, a history of specific joint injury, usually related to sports and recreational activities, is an important risk factor for knee and hip disease.20,21 In the knee in particular, studies showing an association of osteoarthritis with total meniscectomy and meniscal pathology in general highlight the importance of an intact meniscus in preserving the structural integrity of the surface cartilage in this joint.22

Decreased strength and proprioception have been demonstrated in patients with osteoarthritis and likely play a role in pathogenesis of the disease. Patients with radiographic changes of osteoarthritis and no pain have decreased muscle strength in the affected leg, and decreased proprioception has been demonstrated in unaffected knees of patients with unilateral disease.23,24 In addition, local injection to relieve pain only partially improves muscle activity and proprioceptive and gait defects.25 The importance of muscle strength and proprioception to the health of normal cartilage has been further suggested in studies demonstrating cartilage thinning after spinal cord injury.26

Many patients with osteoarthritis have a family history of the disorder, and multiple genetic factors may be responsible for various forms of osteoarthritis.26-28 Osteoarthritis with finger joint involvement in women is probably the best recognized form of arthritis with familial associations,21 but hereditary factors are also important in osteoarthritis of the hip.29-31 Metabolic abnormalities related to the hereditary component of osteoarthritis have been found in a number of studies, including genetic linkages to collagen genes, estrogen receptors, vitamin D receptors, and iron metabolism. The significance of these findings in relation to osteoarthritis in the general population is uncertain. Many different chromosomal markers have been associated with various patterns of osteoarthritis, suggesting that the genetic component in osteoarthritis most likely involves multiple genes. Even the association of decreased muscle strength with the development of osteoarthritis of the knee appears to have a significant genetic component.32

In addition to the known heritable and acquired joint dysplasias that cause secondary osteoarthritis, subclinical degrees of dysplasia may be a factor in patients with primary osteoarthritis, particularly of the hip.33-35

NORMAL ARTICULAR CARTILAGE

Articular cartilage is specialized connective tissue that covers the weight-bearing surfaces of diarthrodial joints. It is composed of sparsely scattered cells (chondrocytes) within an extracellular matrix composed of collagen, proteoglycans, and water, with a very small component of calcium salt.36 Most of the collagen in cartilage is type II collagen, which is arranged in thick bundles and is parallel to the surface of the car-
tilage in outer portions and more perpendicular to the surface in deeper layers. This arrangement of collagen serves as a limiting membrane, distributes compressive forces, and tethers the uncalcified cartilage to the more basilar calcified cartilage and subchondral bone.

The proteoglycan component of the matrix of articular cartilage is composed predominantly of a large molecule called aggrecan, which consists of a large core protein with covalently attached side chains of glycosaminoglycans, most of which are chondroitin sulfate and keratan sulfate. A link protein connects aggrecan to hyaluronic acid, a long, unbranched polysaccharide molecule that can bind several hundred aggrecan molecules. This aggregate of aggrecan molecules forms a very large molecule with a molecular weight of 100 million daltons or more. The molecule has a high fixed negative charge, which allows the retention of large amounts of water.

The collagen matrix and hydrophilic proteoglycan component form a resilient tissue that holds water under pressure and is capable of dissipating much of the force of weight bearing, protecting soft tissues and subchondral bone.

In normal cartilage, the turnover rate of collagen is relatively slow, whereas proteoglycan turnover is rapid. The normal turnover of these matrix components is mediated by the chondrocytes, which synthesize the components and the proteolytic enzymes responsible for their breakdown. Chondrocytes are, in turn, influenced by a number of factors, including polypeptide growth factors and cytokines, structural and physical stimuli, and even the components of the matrix itself.

**PATHOLOGIC CHANGES IN OSTEOARTHRITIS**

Osteoarthritis affects all the structures within the joint. Although previous research focused primarily on changes in the articular cartilage, more recent studies have highlighted the importance of the subchondral bone, ligaments, periarticular muscles, and nerves in contributing to an environment in which cartilage is subject to abnormal mechanical stress. Pathologic findings seen in articular cartilage include a loss of homogeneity, as well as disruption and fragmentation of the surface. Uneven staining for proteoglycans is seen in the matrix, and the deeper layers of cartilage are invaded by capillaries from the calcified cartilage. Chondrocytes, which exist as isolated cells in normal cartilage, begin to proliferate and are found in large clusters and clones, and osteophytes are formed, which are covered by irregular hyaline and fibrocartilage (see Figure 1).

In early osteoarthritis, the water content of diseased cartilage increases and the cartilage swells, and the collagen fibers are usually smaller and not as tightly organized. The proteoglycan content of cartilage decreases markedly as disease progresses, with shortening of the glycosaminoglycan chains and impaired molecular aggregation.

Osteoarthritic cartilage is characterized by an increase in anabolic and catabolic activity. In the early stages, the synthesis of collagen, proteoglycans, and hyaluronate is increased, and chondrocytes tend to replicate. At the same time, the synthesis of degradative enzymes such as collagenase, stromelysin, gelatinase, and hyaluronidase is increased, whereas some of the substances that inhibit cartilage destruction are themselves destroyed or inhibited. In the later stages, the anabolic activities of the chondrocytes become insufficient to keep up with the degradative process. The final result is a matrix that is less structurally sound and less well organized on a macromolecular basis, decreasing the ability of articular cartilage to withstand the forces required of it.

The biochemical and metabolic changes in cartilage that are considered to be potential etiologic factors in osteoarthritis include abnormalities in collagen structure, crystal deposition, inflammatory mediators, and chondrocyte metabolism. The discovery of a familial form of osteoarthritis associated with a specific genetic defect in collagen has led to speculation that similar abnormalities in collagen or other structural components of car-

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Figure 1  Microscopic appearance of normal articular cartilage (a) and osteoarthritic (b) articular cartilage. In normal cartilage, the cartilage surface is smooth and chondrocytes are regularly arranged, mostly as single cells; the background proteoglycan staining is homogeneous; and the subchondral bony plate is intact. In osteoarthritis, there is splitting fissuring of the surface, proliferation and clustering of the chondrocytes, and decreased and irregular staining of the background proteoglycan.
Role in the relationship between obesity and osteoarthritis. Both calcium pyrophosphate dihydrate and basic calcium phosphate crystals have been associated with osteoarthritic cartilage. In vitro measurement of the by-products of cartilage breakdown suggests that these crystals magnify the degenerative process by stimulation of mitogenesis in fibroblasts and secretion of proteases by cells that ingest the calcium-containing crystals.

The reasons for the increased anabolic and catabolic activities of chondrocytes in osteoarthritic joints are not well understood. Mechanical forces likely stimulate chondrocytes to produce a number of inflammatory mediators that result in damage to the extracellular matrix, including interleukin-1 (IL-1), IL-6, IL-8, IL-17, IL-18, monocyte chemotactic protein, and nitric oxide and other reactive oxygen species. In addition, chondrocytes produce growth factors, including bone morphogenic protein-2 (BMP-2), BMP-7, insulin-like growth factor 1, and transforming growth factor-β, which can allow for repair and remodeling of injured matrix. Age-related changes in chondrocytes, along with genetic factors, and reactive nitrogen species all contribute to the defect in remodeling seen in osteoarthritis. In addition, the finding of increased leptin levels in cartilage and synovial fluid of osteoarthritic joints has suggested a role for this substance in the development of osteoarthritis and in the relationship between obesity and osteoarthritis. Whether the observed abnormalities in these factors are etiologic or merely represent the response of the chondrocyte to other injury is not yet known. The role of inflammation and the potential for damaged cartilage to invoke a more intense inflammatory response than normal cartilage are also areas of ongoing research.

The pain of osteoarthritis appears to be derived from inflammation of soft tissue structures surrounding bone, as well as from edema of subchondral bone. In addition, edema in subchondral bone is associated with further progression of cartilage damage over time.

Diagnosis

Characteristic radiographic features are usually considered essential for diagnosis but should be corroborated by the presence of compatible symptoms [see Figure 2]. Laboratory studies are useful in the evaluation of patients with osteoarthritis only in that they help to exclude other diagnoses. Thus, the erythrocyte sedimentation rate (ESR), rheumatoid factor level, and routine hematologic and biochemical parameters should be normal in patients with osteoarthritis unless the osteoarthritis is attributable to comorbid conditions. Synovial fluid from involved joints is noninflammatory, with leukocyte counts of less than 2,000/mm³ in most patients. The presence of birefringent calcium pyrophosphate dihydrate crystals is diagnostic of a separate process that frequently is concurrent with typical osteoarthritis. Basic calcium phosphate crystals, which are not birefringent, may be seen frequently in typical osteoarthritis if special stains are used.

Even though some patients have multiple joint involvement, specific joints should be considered individually so that no important problem-causing nonarticular or superimposed process is overlooked.

CLINICAL MANIFESTATIONS

General

Typical symptoms of osteoarthritis include pain, stiffness, swelling, deformity, and loss of function. Pain is usually chronic and localized to the involved joint or joints or referred to nearby areas. Pain may be mild or moderate early in the disease but tends to worsen gradually over many years. Most of the pain is made worse with activity and improves with rest. Morning stiffness is not as prolonged as in patients with inflammatory diseases; morning stiffness in patients with osteoarthritis usually lasts less than an hour. Many patients complain of stiffening, or so-called gelling, during the day, particularly after sitting for extended periods. Swelling tends to be mild or moderate and is often related to bony enlargement rather than soft tissue edema. Deformity and loss of function are later manifestations, occurring after many years of disease.

Physical findings in osteoarthritis include crepitus, pain on motion, bony enlargement, and periarthritis tenderness. Synovial effusions may be present, particularly in the knee. Erythema and warmth are unusual and should suggest the presence of coexistent crystal-induced inflammation or other conditions. In more advanced disease, limited range of motion, deformity, and instability may become more prominent findings.

Specific Joint Involvement and Complications

Osteoarthritis has a characteristic pattern of involvement in most patients. Frequently involved joints include the distal and proximal interphalangeal joints, as well as the first carpometacarpal joints in the hands, the cervical and lumbar spines, the carpal joints of the hands, and the cervical spine.
hips, the knees, and, less commonly, the small joints of the feet or the acromioclavicular joint. The wrists, metacarpophalangeal joints, elbows, shoulders, and ankles are usually not affected unless there is a history of injury to the specific joint, occupational overuse, or underlying condition that might be a cause of secondary osteoarthritis.

**Hands** The most commonly affected joints in the hands in patients with osteoarthritis are the distal and proximal interphalangeal joints, in which bony enlargement occurs (i.e., Heberden and Bouchard nodes, respectively) [see Figures 3 and 4]. Enlargement of these joints progresses slowly over many years, is frequently familial, and occurs most often in middle-aged or elderly women. Individual joints may go through inflammatory phases with redness and increased swelling and pain, most of which eventually subsides to a bony enlargement. Small gelatinous cysts may develop over the dorsal aspect of the distal interphalangeal joints and either persist or resolve spontaneously. Many patients with Heberden and Bouchard nodes have very little pain most of the time and therefore may not seek medical attention. The carpometacarpal joint of the thumb is another frequently involved joint, either by itself or along with the more distal joints; in such cases, patients experience pain, bony enlargement, and limited motion of the thumb.

**Knees** Osteoarthritis frequently affects the knees and may be a cause of significant disability. Most patients present with pain that is worse with activity and improves with rest; they report difficulty getting out of chairs or going up steps. Patients with osteoarthritic knees will almost always have crepitus, limited motion, and pain on motion; effusions may or may not be present. In more advanced disease, bony enlargement, instability, and varus angulation may be present. Many patients have involvement of the patellofemoral compartment, but isolated disease in this area should suggest the presence of calcium pyrophosphate deposition disease.

**Hips** Osteoarthritis of the hips is another common cause of significant pain and disability [see Figure 5]. Most patients experience a progressive disabling pain, usually in the upper thigh or inguinal region, sometimes radiating to the knee. Pain is worse with ambulation and may cause the patient to limp. Patients may also complain of difficulty with activities such as tying shoes, and limited hip motion is found on physical examination.

**Spine** Osteoarthritis of the cervical and lumbar spine is referred to as spondylosis. Involvement of the intervertebral disk spaces or the posterior spinal facet joints may cause chronic back pain, the knees, and, less commonly, the small joints of the feet or the acromioclavicular joint. The wrists, metacarpophalangeal joints, elbows, shoulders, and ankles are usually not affected unless there is a history of injury to the specific joint, occupational overuse, or underlying condition that might be a cause of secondary osteoarthritis.

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**Spine** Osteoarthritis of the cervical and lumbar spine is referred to as spondylosis. Involvement of the intervertebral disk spaces or the posterior spinal facet joints may cause chronic back
or neck pain that worsens with activity and improves with rest. Disk degeneration may be complicated by protrusion of the nucleus pulposus, causing nerve root compression with radicular pain or muscle weakness. In patients with extensive degenerative changes with fibrosis and osteophytes, stenosis of the spinal canal can occur, resulting in chronic cord compression in the cervical spine or compression of the cauda equina in the lumbar region. Lumbar spinal stenosis, causing chronic radicular leg pain that is worse with activity and better with rest (neurogenic claudication), is a common complication in elderly patients. A variant of spinal osteoarthritis occurring in the thoracic spine, known as diffuse idiopathic skeletal hyperostosis (DISH), is characterized by extensive bridging osteophytes and may cause loss of motion but little pain.

**Radiologic Features**

Typical radiographic findings in osteoarthritis include joint space narrowing, subchondral bone sclerosis, subchondral cysts, and osteophytes (bony spurs) [see Figure 5]. Joint space narrowing, resulting from loss of cartilage, is often asymmetrical and may be the only finding early in the disease process. In weight-bearing joints such as the knees, narrowing may be seen only in a standing view and may be missed in a radiograph obtained with the patient in the recumbent position. In more chronic disease, the hypertrophic features of subchondral sclerosis and osteophyte formation become more prominent, and subluxations or fusion of the joint may become apparent in more severely affected joints. In the small interphalangeal joints of the fingers, central erosions may be seen within the joint space; these erosions should be easily distinguishable from the periarticular erosions of rheumatoid arthritis.

**Differential Diagnosis**

Because of the high frequency of incidental radiographic changes in the general population, it is important not to attribute all musculoskeletal pain to osteoarthritis, even in patients with radiographic abnormalities. Alternative diagnoses should be made or coexistent conditions suspected in patients who are considered to be at low risk for osteoarthritis (e.g., younger patients) or in those who present with atypical pain patterns or atypical joint involvement. Patients with a relatively sudden onset of pain or with severe pain early in their presentation most often have something other than osteoarthritis. Problems in the wrists, elbows, shoulders, or ankles should raise concerns about other types of arthritis or secondary types of osteoarthritis.

Crystal-induced arthritis should always be considered in patients with acute pain, particularly if swelling and erythema are prominent. Calcium pyrophosphate deposition disease is common in the knees and hips and often coexists with osteoarthritis. Other joints frequently involved are the wrists and shoulders. Detection of chondrocalcinosis on x-ray or of crystals in synovial fluid confirms the diagnosis. Gout usually affects foot and ankle joints in early disease and is not often confused with osteoarthritis, but involvement of the knees is common later in the disease course. In addition, elderly women with Heberden and Bouchard nodes in the hands may have superimposed attacks in these joints as an initial manifestation of gout. Thus, examination of fluid from these joints for urate crystals may be essential in differentiating gout from an inflammatory flare of erosive osteoarthritis.

Rheumatoid arthritis can usually be distinguished from osteoarthritis on the basis of a different pattern of joint disease, more prominent morning stiffness, and soft tissue swelling and warmth on physical examination. In some patients, the patterns of joint disease may overlap, particularly in the proximal interphalangeal joints, hips, and knees. Thus, in some patients, the presence of an elevated ESR, a high-titer rheumatoid factor measurement, or periarticular erosive changes may be the only way to distinguish these two common conditions.

Polymyalgia rheumatica is a disease of the elderly and is often seen in patients with underlying osteoarthritis. Patients typically have a change in the pattern of pain, more localized to the shoulder and hip girdles, with few peripheral joint symptoms. Morning stiffness is a prominent feature, and the diagnosis is usually more likely if the ESR is markedly elevated. However, because modest elevations of ESR are seen in many normal elderly individuals, the differentiation of this condition from osteoarthritis is often difficult. In some patients, a rapid response of symptoms to a low dose of corticosteroid is helpful in making a diagnosis.

Ankylosing spondylitis is usually a disease that first manifests in young adulthood and should not be confused with spinal osteoarthritis. However, some patients have only mild levels of pain and may not seek medical attention until later years. In such patients, the radiographic changes in the cervical and lumbar spine in the two conditions should make differentiation between them relatively easy.

Psoriatic arthritis, when present in a classic distribution in the distal interphalangeal joints of the fingers, may mimic Heberden nodes. Psoriatic arthritis usually occurs in younger persons and is more common in males, but differentiation between psoriatic arthritis and Heberden nodes may still be difficult. In young patients with arthritis of the distal interphalangeal joints, a careful search for psoriatic skin lesions and nail changes is essential. On physical examination, the swelling of involved joints is usually greater in the soft tissues, with less bony enlargement. Radiography will usually show more erosive changes and fewer osteophytic changes than in typical osteoarthritis.

Disorders of bone near joints can be confused with osteoarthritis. Osteonecrosis of the hip, knee, or shoulder may cause pain and restricted motion without significant signs of inflammation. Radiographs may be normal initially, and follow-up radiographs or magnetic resonance imaging may be necessary to differentiate this condition from osteoarthritis. Paget disease or osteoporotic fractures may cause pain in the back and hip girdle that is similar to that of osteoarthritis, although the pain is often more severe and acute in patients with fractures.

Nonarticular pain syndromes involving tendons, bursae, peripheral nerves, and internal joint structures may cause pain similar to that of osteoarthritis. Examples include de Quervain tenosynovitis or carpal tunnel syndrome in the hand, trochanteric bursitis or meralgia paresthetica in the hip, anserine bursitis or meniscal tears in the knee, and planter fasciitis and interdigital neuromas in the feet. Knowledge of nonarticular pain syndromes and of the characteristic patterns of symptoms and physical findings in each is essential to diagnosing these and differentiating these syndromes from osteoarthritis in the same area.

**Management**

There is no cure for osteoarthritis, and no therapy is known to prevent or retard the degenerative biologic process in articular cartilage. Thus, the treatment of osteoarthritis is focused primarily on relieving symptoms and improving function.
Treatment decisions should be based on the severity and distribution of joint involvement, considered in the light of the patient’s other medical problems that might affect the safety and effectiveness of any chosen therapy [see Table 2].

NONPHARMACOLOGIC MEASURES

Nonpharmacologic measures that have the potential to improve outcomes in osteoarthritis include patient education, physical and occupational therapy assessment and interventions, exercise, weight loss, and dietary measures. Exercise, in particular, should be a part of the therapeutic regimen in every patient. Quadriceps weakness contributes significantly to disability in patients with osteoarthritis of the knee, and exercises designed to strengthen quadriceps have the potential to lessen pain and disability.34 In addition, aerobic exercise, such as a walking program, can improve function and reduce pain. Most studies of patients with osteoarthritis have found that regular activity is associated with a better outcome.35,36 However, compliance with exercise programs is often low, and regular supervised follow-up may be helpful.

The role of obesity as an etiologic factor in osteoarthritis of the knee is well established, and some data suggest that weight loss may reduce the risk of development of symptoms in patients predisposed to osteoarthritis. A 2004 study demonstrated that a program of weight loss combined with exercise was more effective than either intervention alone.37 In addition, epidemiologic studies have suggested a role for adequate dietary vitamin C, D, and K intake in reducing the risk of progression of established osteoarthritis.38,39 In some patients, measures designed to alter the biomechanical forces on diseased joints should be considered, including patellar taping and the use of wedged insoles, bracing, canes, and crutches.

PHARMACOLOGIC THERAPY

The primary goal of drug therapy in osteoarthritis is to relieve pain. Acetaminophen may be as effective as nonsteroidal anti-inflammatory drugs (NSAIDs) in some patients, although in many studies, acetaminophen demonstrated only marginal efficacy for osteoarthritis.40-42 In most cases, up to 3,000 to 4,000 mg of acetaminophen a day can be given. Doses should be limited in patients with exposure to other potentially hepatotoxic substances. In particular, patients who take acetaminophen regularly should be advised to limit alcohol ingestion and be warned about the increased risk of acetaminophen hepatotoxicity in heavy drinkers. Opioids are generally avoided in osteoarthritis but may be useful in selected patients. These agents should be used with caution in elderly patients. Tramadol, a centrally acting analgesic with dual mechanisms, may give relief comparable to that achieved with acetaminophen and codeine. Topical capsaicin may be useful in some patients, especially those with involvement of the knees and hands; studies of topical NSAIDs have shown limited efficacy.43

A number of alternative or complementary therapies have been investigated for the treatment of osteoarthritis. These studies have been poorly controlled or limited, however, and little evidence supports the widespread use of most integrative therapies at present.44-46 Recent studies of acupuncture for pain relief in patients with osteoarthritis have shown variable levels of improvement, including some benefit compared with no therapy, sham procedure, or minimal acupuncture, but the magnitude of improvement in these trials has been small.47-50

NSAIDs are useful in osteoarthritis mostly for their analgesic effects; in most patients, they are more effective than acetaminophen.71-73 Unfortunately, NSAIDs are associated with hypertension, fluid retention, and renal compromise. They are also associated with an increased risk of gastric ulcers and bleeding, particularly in patients with a history of gastrointestinal disease, those on concomitant steroids or anticoagulants, and those older than 65 years. Strategies to reduce gastrointestinal toxicity include the use of lower doses of NSAIDs or concomitant use of misoprostol, histamine2 receptor antago-

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Useful for What or Whom?</th>
<th>Measure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpharmacologic</td>
<td>All patients</td>
<td>Exercise</td>
<td>Range of motion and strengthening of muscles around affected joints</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight loss</td>
<td>Particularly valuable in patients with involvement of weight-bearing joints</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dietary measures</td>
<td>Adequate intake of calcium, vitamin C, and vitamin D</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Most or all patients</td>
<td>Simple analgesics</td>
<td>Acetaminophen, tramadol, narcotics in selected cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAIDs</td>
<td>Nonselective NSAIDs for patients at low risk for GI complications; otherwise, consider addition of misoprostol, a proton pump inhibitor, or an H2 antagonist or use of a cyclooxygenase-2–specific NSAID (coxib)</td>
</tr>
<tr>
<td>Ancillary medical and surgical</td>
<td>Selected joints or patients</td>
<td>Splints</td>
<td>Specific for each joint</td>
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<td></td>
<td></td>
<td>Canes or other orthotics</td>
<td>Patellar taping, wedged shoe insoles for knee OA in selected patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corticosteroid injections</td>
<td>Knees, fingers; other joints in selected cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyaluronic acid injections</td>
<td>Knees in some patients</td>
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<tr>
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<td></td>
<td>Arthroscopic surgery</td>
<td>For patients with mechanical symptoms or findings</td>
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<tr>
<td></td>
<td></td>
<td>Osteotomy</td>
<td>Knees in selected patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total joint replacement</td>
<td>—</td>
</tr>
</tbody>
</table>

NSAIDs—nonsteroidal anti-inflammatory drugs  OA—osteoarthritis

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treated in animal models of osteoarthritis.86,87 Thus, when prescribing NSAIDs of all classes, clinicians should weigh the potential cardiovascular risks against anticipated benefits and consider issues such as dose and comorbid conditions.

Intra-articular corticosteroid injections may be useful in treating selected joints, particularly during exacerbations characterized by increased pain and effusion, and injections in symptomatic knees every 3 months may be a safe and effective means of reducing pain and improving function over longer periods.79 Most controlled studies have shown benefit compared with placebo, although the duration of benefit has been relatively short (i.e., 1 to 6 weeks).80,81 Intra-articular hyaluronic acid derivatives, given in a series of three to five weekly injections, have been shown to be superior to placebo in most studies and may be useful in relieving pain in selected patients with less advanced disease, but treatment effect appears to be relatively small.82-84

Surgery

In patients with badly damaged knees and hips, total joint replacement is an effective option. Almost all patients experience significant pain relief, and some have improved range of motion. Joint loosening and infection are potential late complications in prosthetic joints but are uncommon. Arthroscopic debridement of affected joints is no better than placebo in untreated patients with osteoarthritis of the knee.85 Thus, this procedure should be reserved for patients with mechanical symptoms suggesting internal derangement. Realignment of a degenerative knee to allow redistribution of forces is sometimes attempted by a high tibial wedge osteotomy, particularly in younger patients with valgus deformities.

Biologic approaches to the surgical treatment of osteoarthritis have been explored. These include local enhancement of bone marrow progenitor cells and various forms of cartilage transplantation. In addition, stem cell transplantation has been investigated in animal models of osteoarthritis.86,87

Protecting cartilage (disease modification)

Therapies with potential to prevent or retard the progression of articular cartilage breakdown have received a great deal of attention in recent years, but studies have been limited by the lack of clear definition of disease modification or chondroprotection in clinical trials.88,89 Agents considered to have so-called chondroprotective potential include tetracyclines, protease inhibitors, antiresorptive agents (i.e., bisphosphonates, calcitonin), glycosaminoglycan compounds, growth factors, and cytokine inhibitors. Oral glucosamine and chondroitin sulfate have been promoted as health food supplements to improve cartilage, but most of the clinical studies with these agents have demonstrated only modest pain relief, compared with placebo; studies to assess the effect on cartilage are ongoing.90-94 Inconsistent dosages in different studies and lack of standardization of available preparations have complicated assessment of these agents’ value.

Tetracyclines have been shown to reduce the severity of osteoarthritis in animals, probably by inhibiting metalloprotease activity, and early trials in humans have shown potential for disease modification.95 Other approaches to disease modification being investigated in animal models include other agents that inhibit metalloproteases or nitric oxide synthase inhibitors.

Prognosis

Osteoarthritis is a slowly progressive condition with a variable prognosis.9 Radiographically, most joints will either remain stable or gradually worsen over a 5-15-year period. In most patients, symptoms evolve over many years and may spontaneously remit for long periods of time without explanation. Progression of osteoarthritis of the hand is particularly hard to measure because pain levels frequently improve after involved joints become fused. Disease may progress more rapidly in the hips and knees of older women with osteopenic bone. However, in general, predicting the prognosis in patients with osteoarthritis is difficult. Risk factors for worsening status include increased age, increased body mass index, proinflammatory deficient, and pain intensity, whereas greater muscle strength, mental health, self-efficacy, social support, and aerobic exercise are associated with better outcomes.96

The author has received grants for clinical research from Abbott Laboratories, Amgen, Inc, Bristol-Myers Squibb Co., and Centocor, Inc.

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April 2007 Update

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RHEUMATOLOGY:X Osteoarthritis–8
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Acknowledgment

Figure 1 Courtesy of Richard Hard, M.D.