CHAPTER 11

Osteoarthritis
A. Clinical Features

PAUL DIEPPE, MD

- Osteoarthritis (OA) is the most common form of joint disease in humans.
- The most commonly affected are apophyseal joints of the cervical and lumbar spine, interphalangeal joints of the hand, the thumb base, the first metatarsophalangeal joint, the hips, and the knees.
- Osteoarthritis is strongly age related. Additional risks include family history, female sex, obesity, and trauma.
- The symptoms of OA are pain, short-lasting stiffness, cracking of joints, joint swelling, fatigue, and functional limitation.
- Osteoarthritis is characterized on physical exam by firm swelling around the joint line, crepitus, and restricted range of motion.
- Diagnosis of OA can usually be made by history and physical exam, but radiographs demonstrating joint space loss, osteophytes, and changes in the subchondral bone are diagnostic.

Osteoarthritis (OA) is the most common form of joint disease in humans. Our ancestors' skeletons show that it has been with us for many centuries. However, it was only differentiated from other forms of arthritis about 100 years ago (1), when a combination of pathological and radiographic studies made it clear that there were two quite distinct types of synovial joint damage: atrophic arthritis, in which there is periarticular osteoporosis and erosive changes, in addition to cartilage loss; and hypertrophic arthritis, in which the cartilage loss is accompanied by an increase in bone density and bone formation around the joint.

The atrophic subset was subsequently differentiated into a variety of infectious and inflammatory conditions, including rheumatoid arthritis (RA). Hypertrophic arthritis is what we now know as OA. It is clear that this too includes a variety of different conditions, but we have made less progress in our understanding of this group, and the differentiation of distinct entities has proved elusive. *Osteoarthritis*, then, is a term that describes a heterogeneous group of common conditions, with similar pathological and radiographic features.

EPIDEMIOLOGY

Osteoarthritis is a strongly age-related disorder. It is uncommon before the age of 40, but its prevalence rises rapidly with age thereafter, such that most people over the age of 70 have the pathological changes of OA in some of their joints (although they may remain asymptomatic).

The most important risk factors for OA are shown in Table 11A-1. But, as indicated, some risk factors are more important for OA of a particular joint than others. For example, OA of the knee is strongly associated with women and obesity, and is more common in blacks than whites, whereas hip OA has a more equal sex incidence, a less strong association with obesity, and is rare in Chinese people.

CLINICAL FEATURES

Osteoarthritis is, by definition, a disorder of synovial joints. It can affect any one of the 200 or so synovial joints in the body, but whereas it is common in some, it rarely affects others. The most frequently affected sites are the apophyseal joints of the cervical and lumbar spine, the interphalangeal joints of the hand, the thumb base, the first metatarsophalangeal joint, the knee and the hip. Shoulders, ankles, and metacarpophalangeal joints are amongst the less common sites of OA.

Osteoarthritis is also a focal disease of joints. Unlike inflammatory arthropathies, it does not always affect the whole joint. For example, in the knee the most common parts to be affected are the medial tibiofemoral and lateral patellofemoral compartments, and the superior pole of the hip is the most likely area of that joint to be damaged.

TABLE 11A-1. RISK FACTORS FOR OSTEOARTHRITIS.

Increasing age (all sites)
Female sex or gender (some sites, particularly knee and hand)
Race or ethnicity (variable at different joint sites)
Genetic predisposition (all sites)
Obesity (most sites, but more marked for the knee than other joints)
Trauma, and some occupations involving repetitive activities (specific sites)

How can we explain this? If the OA process is driven by mechanical factors, one plausible hypothesis is that it is an age-related disorder of evolution (2). Our musculoskeletal system evolved to suit our ancestors, who walked around on four legs and did not have a prehensile grip. In evolutionary terms, we stood up and started to grip things between fingers and thumbs a relatively short time ago, so that the skeleton has not had time to adapt to these changes in posture and joint use. One result of this is that the shape of certain parts of our joints, such as the superior pole of the hip, are not well suited to the mechanical stresses that our everyday activities submit them to.

HISTORY

Despite the fact that OA is described as a heterogeneous group of disorders, shared clinical features bind the group together. The two cardinal symptoms of OA are use-related pain, and relatively short-lasting stiffness or gelling of the joints after inactivity.

We know surprisingly little about OA pain—either about the patient experiences of pain or about its pathogenesis. Most people describe pain that is exacerbated by use of the joint, but the discomfort often continues for some time after activity ceases, wearing off slowly. Some people experience particularly severe but short-lasting bouts of pain on a particular movement or activity, and some experience such bouts spontaneously. In others pain can occur at night, disrupting sleep. A wide variety of adjectives are used to describe the pain or discomfort. The amount of pain experienced obviously depends on what people do, and to what extent they avoid particular activities or movements that are most likely to exacerbate it, making the assessment of pain in OA problematic.

Similarly, gelling of joints is a somewhat mysterious symptom. The most common phenomenon seems to be difficulty initiating joint movement after inactivity, epitomized by the problems older people with OA have in "getting started" after sitting down for a while. It is not known what causes this. People may present with a variety of other symptoms, including cracking of joints (audible crepitus), joint locking, swelling, fatigue, and, of course, difficulty with daily activities.

PHYSICAL EXAMINATION

The osteoarthritic joint generally has evidence of mild-to-moderate firm swelling around the joint line, palpable creaking on movement (crepitus), and restricted range of motion with pain at the end of the range. The swelling is usually due to the formation of chondrophytes or osteophytes at the joint margin, and these may be tender. There may also be tenderness over the joint line itself. In some cases there is evidence of mild inflammation, with some warmth over the joint line and an effusion. Other common signs include weakness and wasting of the muscles acting on the joint, and areas of periarticular tenderness. In advanced cases, deformities and instability of the joints are seen.

INVESTIGATIONS

In the majority of cases, OA can and should be diagnosed from the history and clinical signs alone, without recourse to any investigations. It is a localized disorder, without any systemic features, so blood tests are all normal [with the caveat that small increases in serum C-reactive protein (CRP) can occur]. Joint images, including x-rays and magnetic resonance imaging (MRI), are abnormal, reflecting the joint pathology. The plain radiograph is the investigation most frequently used to confirm the clinical diagnosis, and for the definition of the condition for research studies. The main radiographic features of OA are narrowing of the joint space (due to loss of articular cartilage), osteophytes, and a variety of changes in the subchondral bone, including cysts, sclerosis, shape changes, and loss of bone volume (Figure 11A-1) (3).

If synovial fluid is aspirated from a joint with OA, it is generally relatively viscous and translucent in comparison with that from a patient with RA, which tends to be thinner and more opaque due to the higher number of cells related to a greater degree of intra-articular inflammation.

There is a great deal of current interest in another type of laboratory investigation in OA—the search for so-called biochemical markers of the disease process, products of abnormal breakdown or synthesis of connective tissue components in the joint, but such investigations have proved to be of limited value as yet, even as a research tool, and they have no clinical relevance.

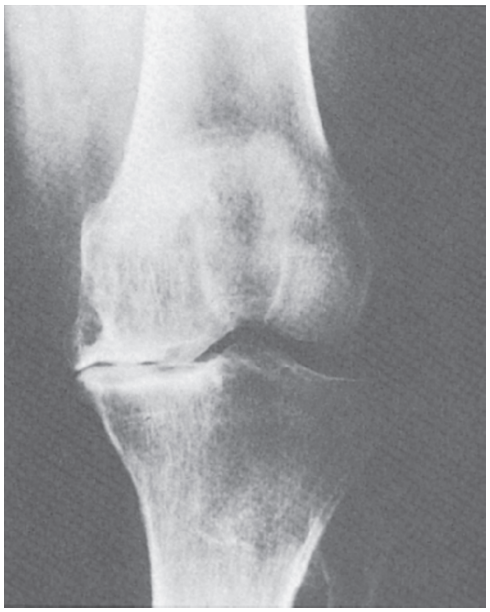


FIGURE 11A-1

Plain radiograph of a typical patient with moderate osteoarthritis of the knee joint. Note the loss of joint space, particularly marked in the medial compartment, caused by loss of articular cartilage, the sclerosis of the underlying subchondral bone, and the osteophyte formation at the joint margin.

DISEASE PATTERNS AND SUBSETS

It has proved difficult to pin down clear disease subsets within what is clearly a spectrum of disorders. This is a major problem for OA research, as the current explosion of interest in the genotype is unlikely to prove valuable until we can describe the phenotype properly.

The main factors that have been considered as indicative of possible subsets have included:

1. The presence or absence of an obvious cause (primary or secondary OA).
2. The distribution between joints and numbers of joints affected (localized or generalized OA).
3. The amount of bone formation around the joints, or, conversely of bone attrition (hypertrophic or atrophic OA), and the related presence or absence of diffuse idiopathic skeletal hyperostosis (DISH).
4. The presence of absence of overt inflammation (inflammatory OA).
5. The presence or absence of chondrocalcinosis (pyrophosphate arthropathy) or of basic calcium phosphate crystal deposition (apatite-associated arthropathy).
6. The rate of progression (rapidly progressive osteoarthritis).

However, a concern is that we have not, as yet, found the most important features of the condition on which to attempt the distinction of subsets. Those of us who are natural splitters of diseases like to talk about distinct subsets when we see patients with OA, such as generalized inflammatory OA, secondary OA of the knee, or pyrophosphate arthropathy, as if these were clear entities. But there is a great deal of evidence to suggest that such patients represent the extremes of the spectrum, rather than distinct disorders. For example, the chances of someone getting secondary knee OA after injury or meniscectomy are dependent on the same set of local and systemic risk factors associated with primary or sporadic cases of knee OA (4). Similarly, most patients with OA and effusions have some crystals in their joint fluid; this is just rather more obvious in some, such as those that we might label as having the condition pyrophosphate arthropathy.

Genetic investigations may help sort out this problem. For example, families who inherit an abnormality in the articular cartilage, such as those with the well-described abnormality of the COL2A1 gene, or those with alkaptonuria, have an uncommon OA phenotype characterized by the involvement of joints not usually affected by sporadic or generalized OA (such as the shoulder) and by more involvement of the lateral than the medial side of the tibiofemoral joint. Similarly, some forms of epiphyseal dysplasia, which can result in an unusual, premature OA phenotype, have been associated with genetic defects of cartilage components, such as COL9A3 (5). This suggests that most sporadic OA may not be caused by intrinsic abnormalities of articular cartilage.

The typical patient with OA is a middle-aged or older person presenting with the gradual onset of discomfort and stiffness in a knee or hip, often accompanied by some back pain, in whom one or both hips or knees are the major sites of joint damage. In some of these cases there is evidence of previous injury or abnormality in the worst affected joint(s).

However, in routine clinical practice, there are a number of other quite different patient archetypes seen, who also get labeled as having OA. These include:

1. Menopausal, inflammatory, nodal, generalized (or erosive) OA. As indicated, this condition, which may be a distinct entity, has been given many different names over the years. It occurs most often in women, beginning around the time of the menopause, and is characterized by the development of pain, swelling, and inflammation in interphalangeal joints of the hand (Figure 11A-2). One or more joints come up at a time and are often red. After a while the pain and inflammation in them settles, leaving the joint swollen, sometimes deformed, and stiff. Bony erosions may develop in the joints, and cystic swellings full of hyaluronan can also appear. These features have led many people to specu-

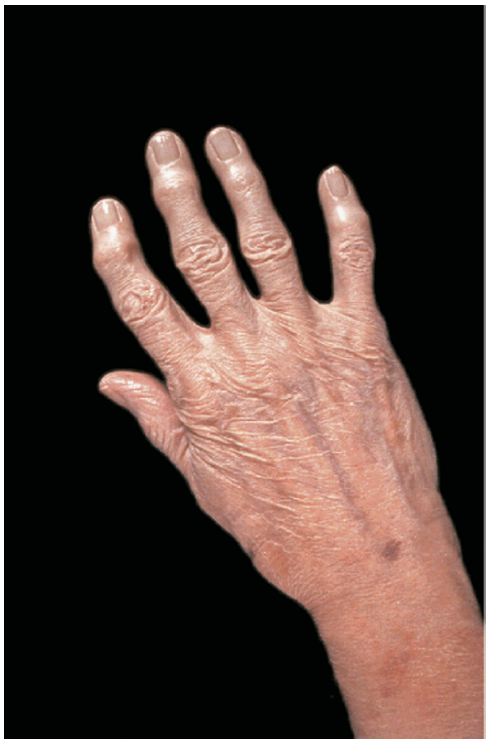


FIGURE 11A-2

Clinical photograph of a patient with nodal, generalized osteoarthritis showing the typical swellings of the distal interphalangeal joints (Heberden's nodes) and of the proximal interphalangeal joints (Bouchard's nodes), as well as squaring of the thumb base due to OA and subluxation of the carpometacarpal joint. (From Women's Health Services, University of Maryland Medical School, with permission.)

late that it is an inflammatory type of arthritis, and to try disease-modifying drugs of the sort used in RA to treat the patients. However, the condition nearly always settles on its own after a few years, and there is no good evidence for the effectiveness of these drugs. Furthermore, the condition does seem to be strongly related to the presence of ordinary OA in the knees and other joints.

2. Diffuse idiopathic skeletal hyperostosis (DISH). This condition is characterized by the formation of bridging enthesophytes in the spine, as well as enthesophytes and osteophytes in peripheral joints, and people with it often have OA (6). The affected joints often "stiffen up" with a marked reduction in the range of motion. DISH is associated with metabolic syndrome and occurs principally in older, obese men or diabetics.

3. Neuropathic arthropathy (Charcot's joints). Denervation of joints, or loss of pain sensation, can result in the development of a destructive form of OA with extensive new bone formation around the joints. This used to be seen mostly in the context of late syphilis (with knee disease), but diabetic neuropathy (with the foot being the principle site affected) or syringomyelia (when the shoulder is the joint most often affected) are now the common causes. So-called Milwaukee shoulder syndrome' or apatite associated destructive arthritis may be a variant of this condition (see Chapter 25D).

4. Rapidly progressive hip or knee OA. As outlined below, the natural history of OA is usually slow. However, in a minority of cases there a rapidly progressive phase of joint damage, often accompanied by more inflammation than is usual, and severe pain. Such cases often come to joint replacement. The cause of this rapid progression is unknown.

DIFFERENTIAL DIAGNOSIS

The diagnosis of OA is easy. The main problem does not come with diagnosing the presence or absence of joint pathology characteristic of OA, it comes in knowing whether the pain and disability is due to those pathological changes or not. As already noted, many people with advanced pathology are asymptomatic, and OA pathology in joints is so common as to be almost normal in older people. So we cannot assume that all those that are symptomatic have pain that is a direct result of their OA pathology. The pain may be referred, it may be due to periarticular problems (such as trochanteric bursitis around the hip or anserine bursitis around the knee), or it may be the result of pain sensitization, causing abnormal sensations with normal activities. Psychological factors, such as anxiety and depression, as well as social problems, such as isolation and coping strategies, are all known to be determinants of pain in people with OA (7).

COURSE, PROGNOSIS, AND OUTCOME

Osteoarthritis is generally thought of as a slowly progressive condition. Its association with age, as well as the loss of articular cartilage—a very obvious pathological feature—has led to it being called *degenerative joint disease* and to all the negativity that goes with such a name, including the concept that it inevitably gets worse and that the joints wear out. This is not the case.

The idea that OA is a spectrum disorder, with relatively distinct clinical entities seen at the ends of the spectrum, including a progressive form, has already been mentioned. Rapidly progressive joint damage is clearly uncommon. Epidemiological data make it is obvious that most OA must stabilize: some 40% of older people have x-ray evidence of significant OA in their hips or knees, and yet less than 5% of older people will ever

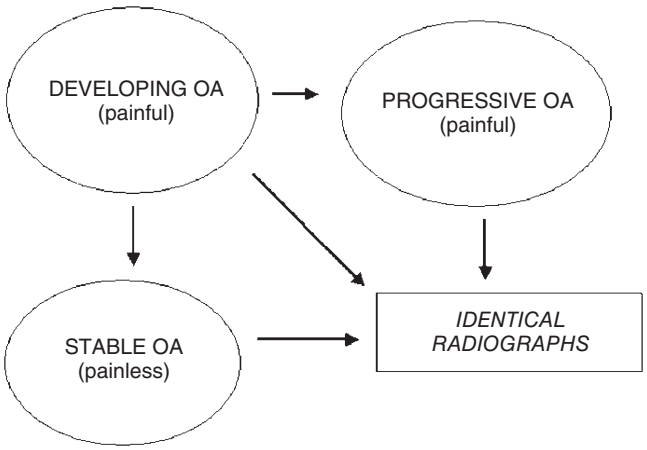


FIGURE 11A-3

Diagram summarizing an hypothesis about OA x-rays and disease progression. This hypothesis, outlined in the text, considers OA to be a phasic disease process that is a response to abnormal joint biomechanics and an attempt at joint repair. While the disease is active, changing joint anatomy, it can cause direct nocioceptive pain. Pain sensitization may also occur, in which case pain may persist when the disease process has ceased to be active. The plain radiograph, the most frequently used investigation in OA, will look the same whether the disease is evolving, inactive, or progressing, and whether the pain is due to direct nocioception, to periarticular problems, or results from peripheral or central pain sensitization.

need a joint replacement. It follows that either the joint damage and/or the symptoms cannot progress in the majority. Most cases stabilize after a period of change in joint anatomy, some progress, and a small minority improve spontaneously (especially hip OA) (8).

It seems likely that OA is a pathological process characterized by phases of activity within the joint, interspersed with periods in which the process is quiescent (9). Perhaps relatively minor degrees of change in biomechanics trigger the process. The process itself can be seen as an attempt of the joint to repair damage; thus, the formation of osteophytes and thickening of the capsule can be seen as the attempt of the joint to splint itself, and the changes in the subchondral bone, which alter joint shape, can be seen as an attempt to normalize load bearing. These processes, which are accompanied by cartilage loss (within this hypothesis cartilage is the innocent bystander) inevitably lead to x-ray changes, but not to symptoms. However, it is also probable that as the joint anatomy is changing pain is generated, along with a change in pain sensitization both in the periphery and centrally, in which case normal movements may become painful, and this activity-related pain (due to sensitization of the pain system) may persist even when the process has become quiescent. If this is the case, it may help us explain the discordance between x-rays and symptoms, as outlined in Figure 11A-3.

Osteoarthritis, then, is not necessarily a progressive disorder, and the prognosis is not inevitably a bad one. However, OA is a disease affecting older people, in whom a combination of advancing years and comorbidities are taking their toll on health. For these reasons, many—perhaps most—people with OA do get worsening of disability over the years, making it appear that their OA has deteriorated. But the comorbidities may be much more important than the OA. For example, in people with OA, walking speed may be as dependent on the presence of a cataract as it is on the joint disease.

REFERENCES

1. Nichols E, Richardson F. Arthritis deformans. J Med Res 1909;21:149–221.
2. Lim K, Rogers J, Shepstone L, Dieppe P. The evolutionary origins of osteoarthritis: a comparative study of hand disease in two primates. J Rheumatol 1995;22:2132–2134.
3. Watt I, Doherty M. Plain radiographic features of osteoarthritis. In: Brandt K, Doherty M, Lohmander S, eds. Osteoarthritis. 2nd ed. Oxford, England: Oxford University Press; 2003.
4. Englund M, Lohmander S. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after menisectomy Arthritis Rheum 2004;50:2811–2819.
5. Nakashima E, Kitoh H, Maeda K, et al. Novel COL9A3 mutation in a family with multiple epiphyseal dysplasia. Am J Med Genet A 2005;132:181–184.
6. Sarzi-Puttini P, Atzeni F. New developments in our understanding of DISH (diffuse idiopathic skeletal hyperostosis). Curr Opin Rheumatol 2004;16:287–292.
7. Steultjens M, Dekker J, Bijlsma J. Coping, pain and disability in osteoarthritis. J Rheumatol 2001;28:1068–1072.
8. Perry G, Smith M, Whiteside C. Spontaneous recovery of the joint space in degenerative hip disease. Ann Rheum Dis 1979;31:440–448.
9. Kirwan J, Elson C. Is the progression of osteoarthritis phasic? Evidence and implications. J Rheumatol 2000; 27:834–836.

CHAPTER 11

Osteoarthritis
B. Pathology and Pathogenesis

FRANCIS BERENBAUM, MD, PHD

- Changes in articular cartilage and subchondral bone are the characteristic histopathological changes of osteoarthritis (OA).
- Osteoarthritis results from a failure of chondrocytes to maintain the balance between degradation and synthesis of extracellular matrix.
- Increased breakdown of cartilage involves proteinases such as matrix metalloproteinase.
- Proinflammatory cytokines synthesized by chondrocytes and synoviocytes may drive production of cartilage-degrading enzymes. Other mediators of inflammation including prostaglandins and reactive oxygen species also contribute to OA pathogenesis.
- Mechanical factors are essential for maintaining normal cartilage homeostasis and mechanical stress contributes significantly to disease initiation and progression.

PATHOLOGY

Osteoarthritis (OA) can be defined as a gradual loss of articular cartilage, combined with thickening of the subchondral bone, bony outgrowths (osteophytes) at joint margins, and mild, chronic nonspecific synovial inflammation. The difference between physiologic aging of the cartilage and OA cartilage is not sharp. However, three cartilage stages can be identified: stage I, normal cartilage; stage II, aging cartilage; and stage III, OA cartilage.

Normal Cartilage

Normal cartilage has two main components. One is the extracellular matrix, which is rich in collagens (mainly types II, IX, and XI) and proteoglycans (mainly aggrecan). Aggrecan is a central core protein bearing numerous glycosaminoglycan chains of chondroitin sulfate and keratan sulfate, all capable of retaining molecules of water. The second component consists of isolated chondrocytes, which lie in the matrix. The matrix components are responsible for the tensile strength and resistance to mechanical loading of the articular cartilage.

Passage of Normal Cartilage to Aging Cartilage

Fissures that develop in cartilage during aging are due mainly to stress fractures of the collagen network. Several structural and biochemical changes involving the noncollagenous component of the matrix occur during aging. These changes alter biomechanical properties of the cartilage that are essential for the distribution of forces in the weight-bearing zone. Glycosaminoglycans are modified qualitatively; they become shorter as the cartilage ages. The concentration of type 6 keratan sulfate (KS) increases during aging, to the detriment of type 4 KS. Also, an age-related reduction in total proteoglycan synthesis after skeletal maturation has been reported. This reduction could be due, at least in part, to a reduction in chondrocyte numbers with advancing age. These quantitative and qualitative changes in proteoglycan reduce the capacity of the molecules to retain water. A prominent feature of aging is the modification of proteins by nonenzymatic glycation leading to the accumulation of advanced glycation end products (AGEs). Once they are formed, AGEs cannot be removed from the collagens, and, therefore, they accumulate in articular cartilage. The accumulation of

AGEs in cartilage leads to inferior mechanical properties. Moreover, chondrocytes can express receptors that are capable of binding AGEs and can modulate cell function. The best characterized AGE receptor is called the receptor for advanced glycation end products (RAGE). Thus, AGEs trigger RAGE on chondrocytes, leading to increased catabolic activity and therefore to cartilage degradation (1). In conclusion, aging cartilage contains less water, which alters the biochemical properties of the cartilage, less chondrocytes, which decreases the capacity of cartilage to synthesize matrix, and altered collagens.

Osteoarthritic Joints

Osteoarthritic joints have abnormal cartilage and bone, with synovial and capsular lesions (2). Macroscopically, the most characteristic elements are reduced joint space, formation of osteophytes (protrusions of bone and cartilage) mostly at the margins of joints, and sclerosis of the subchondral bone. These changes are the result of several histologic phases.

Phase 1: Edema and Microcracks

The first recognizable change in OA is edema of the extracellular matrix, principally in the intermediate layer. The cartilage loses its smooth aspect, and microcracks appear. There is a focal loss of chondrocytes, alternating with areas of chondrocyte proliferation.

Phase 2: Fissuring and Pitting

The microcracks deepen perpendicularly in the direction of the forces of tangential cutting and along fibrils of collagen. Vertical clefts form in the subchondral bone cartilage. Clusters of chondrocytes appear around these clefts and at the surface.

Phase 3: Erosion

Fissures cause fragments of cartilage to detach and "fall" into the articular cavity, creating osteocartilaginous loose bodies and uncovering the subchondral bone, where microcysts develop. The loose bodies cause the mild synovial inflammation of OA. The resulting synovial inflammation often is more focal, though often just as intense, than inflammation that occurs in rheumatoid synovitis. Histologically, OA synovitis is characterized by nonspecific lymphoplasmocytic and histiocytic infiltration.

There is sclerosis of the subchondral bone, due to the apposition of small strips of new bone. Osteophytes form around this zone, their surface covered with fibrilar cartilage. Subchondral sclerosis increases with disease progression. Specific changes in the architecture of the subchondral trabecular bone are due to accelerated bone turnover.

PATHOGENESIS

The physiologic homeostasis of the articular cartilage is driven by chondrocytes, which synthesize collagens, proteoglycans, and proteinases. Osteoarthritis result from a failure of chondrocytes within the joint to synthesize a good quality matrix, in terms of resistance and elasticity, and to maintain the balance between synthesis and degradation of the extracellular matrix.

The change in the quality of the matrix synthesized is due to alterations in the differentiation process of chondrocytes (3). Chondrocyte hypertrophy can contribute to the progression of OA via effects including dysregulation of matrix repair through reduced expression of collagen II and aggrecan, increased expression of type X collagen, upregulation of matrix metalloproteinase 13 (MMP-13), and promotion of pathologic calcification. OA cartilage typically develops foci of maturation of cells to hypertrophic differentiation (4). A recapitulation of embryonic skeletal development also occurs in the deep and calcified zones where the hypertrophic chondrocyte-specific type X collagen is expressed, and in the upper middle zone where type III collagen expression is detected. Chondrocyte dedifferentiation has also been described. The main evidence of chondrocyte dedifferentiation in OA is the presence of types I and III collagens, and the chondroprogenitor splice variant type IIA collagen—none of which usually are present in adult articular cartilage—and the production of greater than normal amounts of type VI collagen.

The imbalance between synthesis and degradation of the extracellular matrix is caused by increasing synthesis of proteinases that breakdown collagens and aggrecans, and decreased synthesis of natural inhibitors of these proteinases, the tissue inhibitor of metalloproteinases (TIMPs). This abnormal chondrocyte synthesis is the result of tissue activation by cytokines, lipid mediators (mainly prostaglandins), free radicals (NO, H_2O_2), and constituents of the matrix itself, such as fibronectin fragments. Activated chondrocytes become capable of synthesizing certain proteinases and proinflammatory mediators. Although the role of the chondrocyte seems to be fundamental, the synovial tissue helps perpetuate chondrocyte activation. Synovial cells phagocytize the fragments of cartilage released into the joint, which causes synovial inflammation. Then, OA synovial cells become capable of producing a range of mediators that are released in the cavity, such as MMPs and cytokines, which in turn can alter the cartilage matrix and activate chondrocytes. Finally, the subchondral bone may

contribute to the degradation of cartilage. Osteoblasts isolated from subchondral OA bone demonstrate an altered phenotype. In comparison to normal osteoblasts, they produce more alkaline phosphatase, osteocalcin, insulinlike growth factor (IGF)-1, and urokinase. OA osteoblast phenotype contributes to cartilage degradation by inhibiting cartilage matrix component synthesis and by increasing MMP synthesis by articular chondrocytes (5).

Enzymes Involved in Cartilage Degradation

The main proteinases involved in the destruction of cartilage in OA are the MMPs (6). There are at least 18 members of this gene family of neutral Zn^{2+} metalloproteinases. Because they are active at neutral pH, the MMPs can act on the cartilaginous matrix at some distance from the chondrocytes. They can be synthesized by chondrocytes and synoviocytes under the influence of cytokines.

Aggrecanase, the enzyme that cleaves the Glu^{373}-Ala^{374} bond of the interspherical domain of aggrecan, also plays a major role in the degradation of the matrix. Two aggrecanases have been cloned. They belong to the MMP family, specifically the ADAMTS (disintegrin and metalloproteinases with thrombospondin motifs) family. They are called aggrecanase 1 (or ADAMTS-4) and aggrecanase 2 (or ADAMTS-11).

The activities of MMPs are strictly controlled by stoichiometric inhibition with specific inhibitors, TIMP1-4. Therefore, the balance between the amounts of MMPs and TIMPs in cartilage determines if cartilage is degraded (7). MMPs produced by the chondrocyte and released into the extracellular matrix are activated by an enzyme cascade involving serine proteinases (plasminogen activator, plasminogen, plasmin), free radicals, cathepsins, and some membrane-type MMPs. This enzymatic cascade is regulated by natural inhibitors, including the TIMPs and the inhibitors of the plasminogen activator. MMP-13 is elevated in OA joint tissues, particularly in articular cartilage, and colocalizes with type II collagen cleavage epitopes in regions of matrix depletion in OA cartilage. The other enzymes that can degrade type II collagen and proteoglycans are the cathepsins. They are active only at low pH and include the aspartate proteinases (cathepsin D) and cysteine proteinases (cathepsins B, H, K, L, and S) that are stored in chondrocyte lysosomes and released into the pericellular microenvironment. Glycosidases also may be important, because proteoglycans are very rich in carbohydrate chains. Although hyaluronidases are not present in cartilage, other glycosidases may contribute to the degradation of proteoglycans.

CYTOKINES

Although OA is often classified as a non-inflammatory disease, numerous studies have shown that inflammatory cytokines provide essential biomechanical signals that stimulate chondrocytes to release cartilage-degrading enzymes. Proinflammatory cytokines synthesized by chondrocytes and synoviocytes bind to specific receptors on chondrocytes. These bound cytokines cause transcription of the MMP genes, and the genes' products are exported from the cell in an inactive form. It is generally accepted that interleukin (IL) 1 is the pivotal cytokine released during inflammation of the osteoarthritic joint (8). Other cytokines are released, including chemokines (IL-8, GRO alpha, MIP-1 alpha and MIP-1 beta). Some of these cytokines and chemokines may be regulatory [e.g., IL-6, IL-8, lymphocyte inhibitory factor (LIF)], or inhibitory (e.g., IL-4, IL-10, IL-13, interferon gamma). IL-1 receptor antagonist, IL-4, IL10, and IL-13 prevent the secretion of some MMPs and may increase the synthesis of TIMPs. In a more general way, IL-4 and IL-13 counteract the catabolic effects of IL-1. Finally, IL-1 alters the quality of the cartilage matrix by causing synthesis of type II and IX collagens to decrease, while increasing the synthesis of type I and type III collagens.

A new family of cytokines, called adipokines (for cytokines produced by adipose tissue), has been recently implicated in the pathophysiology of OA. Adipokines such as leptin, adiponectin, and resistin are detected both in the plasma and in the synovial fluid obtained from OA patients. Various tissues obtained from human OA-affected joints, including synovium, infrapatellar fat pad, meniscus, cartilage, and bone, release leptin and adiponectin. The roles of adopokines in OA pathophysiology remain largely unknown.

Lipid Mediators

The eicosanoids also can take part in chondrocyte activation (9). Prostaglandins, produced after activation of phospholipases A2, cyclooxygenases (mainly the cyclooxygenase-2 isoform) and prostaglandin synthases (mainly the microsomal prostaglandin E synthase-1) by proinflammatory cytokines can favor the synthesis of MMPs by activating the cell via specific cellular or/and nuclear prostaglandin receptors. Among eicosanoids, prostaglandin E2 seems to be the main lipid mediator produced by synovial cells, chondrocytes, and subchondral osteoblasts and involved in cartilage degradation in OA.

Reactive Oxygen Species

Reactive oxygen species (ROS) play a crucial role in the regulation of a number of basic chondrocyte activities,

such as cell activation, proliferation, and matrix remodeling. However, when ROS production exceeds the antioxidant capacities of the cell, an oxidative stress occurs, leading to structural and functional cartilage damages like cell death and matrix degradation (10).

Nitric oxide (NO) is a gas synthesized by way of the oxidation of L-arginine by the NO synthases (NOS). Chondrocytes produce large amounts of NO after upregulation of the iNOS gene by cytokines. Most in vitro studies indicate that NO is partly responsible for the blocking of glycosaminoglycan and collagen synthesis by IL-1, and may contribute to the activation of the latent forms of MMPs. NO also may mediate the IL-1–stimulated synthesis of MMP mRNA and protein, and may contribute to chondrocyte cell death by interfering with survival signals from the extracellular matrix. However, NO may have anabolic and anticatabolic effects in cartilage under certain conditions. Therefore, the actual role of NO in the degradative process of OA is not clear (11).

Matrix Degradation Products

The products of matrix degradation, such as fibronectin fragments, can activate chondrocytes through intergrin-type receptors, causing the synthesis of MMPs. These products can stimulate or activate other factors, such as catabolic cytokines, that amplify the damage. The damage, in turn, enhances the concentrations of the degradation products themselves, as in a positive feedback loop.

Mechanical Stress

Along with chemical mediators, biophysical mediators could also be directly involved in chondrocyte activation in OA. Compressive, but also shear and stretch, stresses occur on cartilage. Interestingly, there is considerable evidence that interactions between biomechanical factors and proinflammatory mediators are involved in the initiation and the progression of OA (12). In vivo studies have shown increased concentrations of inflammatory cytokines and mediators in the joint in mechanically induced models of osteoarthritis. In vitro explant studies confirm that mechanical load is a potent regulator of matrix metabolism, cell viability, and the production of proinflammatory mediators such as NO and prostaglandin E2. Chondrocytes have receptors for responding to mechanical stress and can respond to direct biomechanical perturbation by upregulating synthetic activity or inflammatory cytokines, which are also produced by other joint tissues. Chondrocytes express several members of the integrin family, and these can serve as receptors for fibronectin (alpha 5 beta 1), types II and VI collage (alpha 1 beta 1, alpha 5 beta 1, alpha 10 beta 1), laminin (alpha 6 beta 1), and vitronectin and osteopontin (alpha V beta 3). Some of these receptors are sensitive to prolonged changes in pressure (mechanoreceptors). Injurious static or dynamic compression stimulates depletion of proteoglycans and damage to the collagen network and decreases the synthesis of cartilage matrix proteins, whereas low intensity dynamic compression increases matrix synthetic activity. Certain types of mechanical stress and cartilage matrix degradation products are capable of stimulating the same signaling pathways as those induced by IL-1 and tumor necrosis factor alpha (TNF-alpha). These pathways involve cascades of kinases, including the stress-activated protein kinases (SAPKs), also termed c-Jun N-terminal kinases (JNKs) and p38 MAP kinase, IκB kinases, and phosphatidylinositol-3′-kinase (PI-3K) and NF-κB. Because these pathways may also induce the expression of the genes encoding these cytokines, it remains controversial whether inflammatory cytokines are primary or secondary regulators of the progressive cartilage destruction in OA.

Attempts to Repair Cartilage

There is evidence of attempted repair of the OA-damaged joint, particularly of the cartilage and subchondral bone, at least in the early stages of OA (13). Growth factors involved in the physiological matrix synthesis, such as platelet-derived growth factor, IGF-1, and transforming growth factor beta (TGF-beta), are produced in excess by OA chondrocytes, subchondral bone, and synovial tissues. TGF-beta, IGF-I, and basic fibroblast growth factor have anabolic effects in matrix synthesis, can inhibit the effects of the proinflammatory cytokines, and possess mitogenic properties for the chondrocyte. These growth factors also have a high affinity for matrix. When they are synthesized they become trapped in the cartilage, which acts as a reservoir for these factors. The factors are released when the matrix is broken down, and tend to repair lesions.

There is considerable interest in the role of subchondral bone in this attempted repair. The metabolism of subchondral bone is increased during OA, which leads to the production of growth factors, such as the bone morphogenic protein 2 (BMP-2). Experiments have shown that this protein can repair a cartilaginous defect. However, attempted repair of cartilage defects is in vain for the following reasons: (1) Alterations in the differentiation process of the chondrocytes results in the synthesis of a matrix with poor biomechanical properties. (2) Not enough growth factors and TIMPs are produced to counteract the effect of cytokines and proteinases. (3) The bioavailability of certain growth

factors is decreased (e.g., IGF-I activity is reduced because of excess IGF-binding proteins and receptor desensitization).

Initiation of Osteoarthritis

The initiation of OA is not well understood. It involves local, systemic, genetic, and environmental factors. Numerous mechanical factors can directly or indirectly increase cartilage vulnerability. Experimentally, increased pressure on cartilage alters the matrix architecture, which probably explains the high incidence of knee OA in obese people. The ligaments around the joints become more lax with age, leading to instability and injury. With age, strength gradually decreases and peripheral neurologic responses that protect the joints slow. All these factors contribute to an abnormal distribution of pressure on the cartilage, resulting in shear stress.

Osteoarthritis also may be triggered by changes in the structure of the subchondral bone. This hypothesis is based on the observation that sclerosis of subchondral bone precedes cartilaginous defects in some patients. Repeated microtraumas affecting the joint could provoke microfractures of the subchondral bone that, in turn, may modify the biomechanical qualities of the cartilage in the environment of these microfractures. These changes would cause the bone to synthesize growth factors that can result in the production of osteophytes and osteosclerosis.

Epidemiological studies on the prevalence of OA in women after menopause suggest that one or more hormonal factors are involved in the initiation of OA. Chondrocytes bear estrogen receptors, and stimulation of these receptors triggers the synthesis of growth factors. The plasma concentration of estrogens decreases after menopause, which could result in decreased synthesis of growth factors by chondrocytes. This theory is being examined, particularly in OA of the hand and knee, two sites more frequently affected in this population.

CONCLUSION

The simple hypothesis that a passive deterioration of cartilage is the main cause of OA has given way to a more exciting view (Figures 11B-1, 11B-2). It is clear that the pathogenesis of OA is due to altered chondrocyte phenotype mediated by different autocrine and paracrine signals, leading to the synthesis of many mediators of inflammation and degradation that alter the matrix. Moreover, recent experimental studies emphasize the predominant role of mechanical stresses on chondrocyte activation. It is quite likely that research carried out over the next decade will result in increased understanding of the interaction between biomechanics and molecular biology of chondrocytes, and of the interaction between bone and cartilage in the pathogenesis of OA.

FIGURE 11B-1

Modulation of chondrocyte activation by catabolic pathways. Signaling pathways are activated by the binding of catabolic mediators on specific receptors. Activation of these signaling cascades lead to transcription and post-transcriptional modifications of a set of genes [MMPs, aggrecanases (ADAMTS), cytokines, NO, and prostaglandins]. Some of them may feedback/regulate or amplify these responses. These catabolic factors include biochemical [proinflammatory cytokines, reactive oxygen species (ROS), prostaglandins, ligands for the receptor of advanced glycation end products (RAGE), extracellular matrix (ECM) components] and biophysical factors (mechanical stresses).

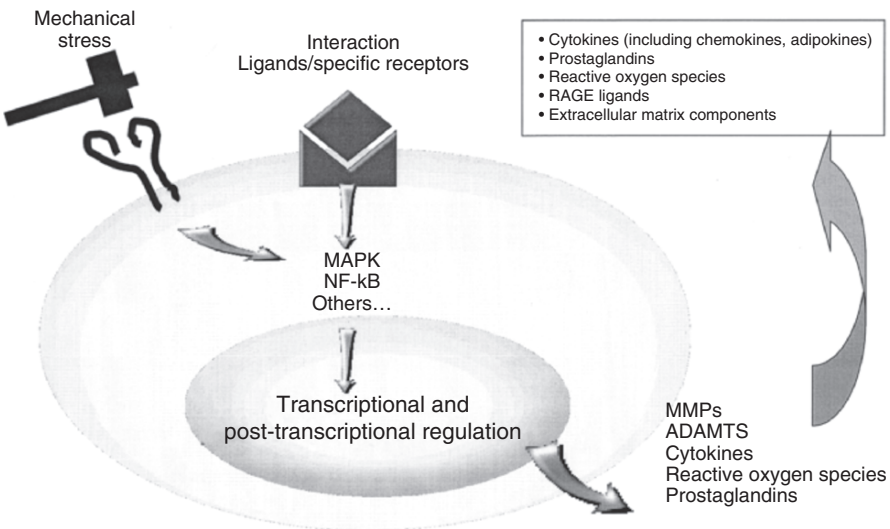
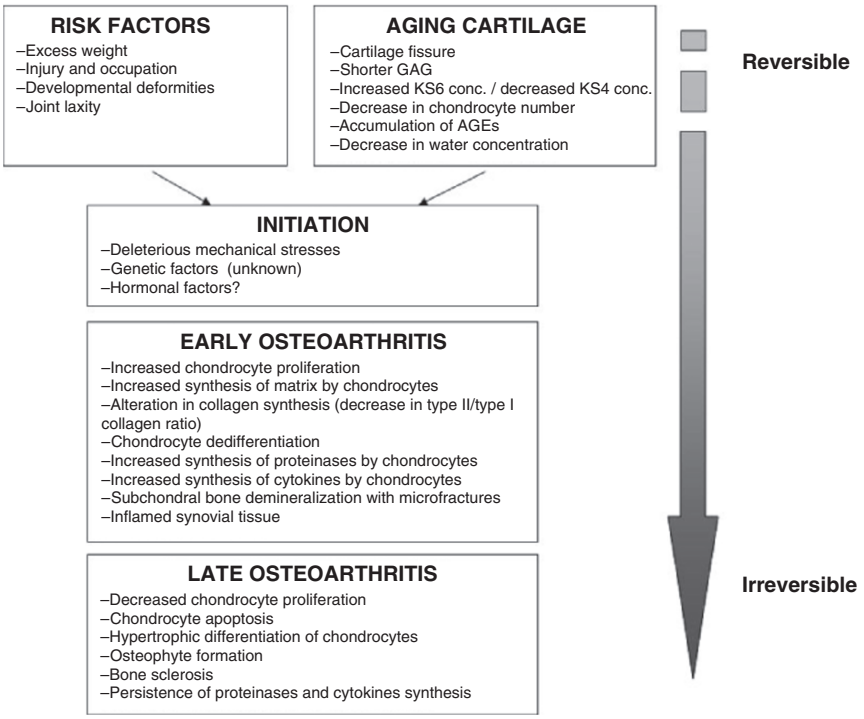


FIGURE 11B-2

Hypothetical model for initiation and perpetuation of osteoarthritis. Accumulation of risk factors on aging cartilage triggers the initiation of the osteoarthritic process. For didactic reasons, two phases are described, early OA and late OA, but the passage from one to the other is progressive and generally lasts many years. Structural treatment of OA should be more efficient at the early stage when chondrocytes keep a high metabolic activity rather than at the late stage when chondrocytes lose their ability to synthesize matrix. Abbreviations: KS, keratan sulfate; AGE, advanced glycation end products.



REFERENCES

1. Loeser RF, Yammani RR, Carlson CS, et al. Articular chondrocytes express the receptor for advanced glycation end products: potential role in osteoarthritis. Arthritis Rheum 2005;52:2376–2385.
2. Pritzker KPH. Pathology of osteoarthritis. In: Brandt KD, Doherty M, Lohmander S, eds. Osteoarthritis. New York: Oxford University Press; 1998;50–61.
3. Goldring MB. The role of the chondrocyte in osteoarthritis. Arthritis Rheum 2000;43:1916–1926.
4. Cecil DL, Johnson K, Rediske J, Lotz M, Schmidt AM, Terkeltaub R. Inflammation-induced chondrocyte hypertrophy is driven by receptor for advanced glycation end products. J Immunol 2005;175:8296–8302.
5. Lajeunesse D, Hilal G, Pelletier JP, Martel-Pelletier J. Subchondral bone morphological and biochemical alterations in osteoarthritis. Osteoarthritis Cartilage 1999;7:321–322.
6. Cawston T. Matrix metalloproteinases and TIMPs: properties and implications for the rheumatic diseases. Mol Med Today 1998;4:130–137.
7. Dean DD, Martel-Pelletier J, Pelletier JP, Howell DS, Woessner JF Jr. Evidence for metalloproteinase and metalloproteinase inhibitor imbalance in human osteoarthritic cartilage. J Clin Invest 1989;84:678–685.
8. Jacques C, Gosset M, Berenbaum F, Gabay C. The Role of IL-1 and IL-1Ra in joint inflammation and cartilage degradation. Vitam Horm 2006;74:371–403.
9. Goldring MB, Berenbaum F. The regulation of chondrocyte function by proinflammatory mediators: prostaglandins and nitric oxide. Clin Orthop 2004;(Suppl):S37–S46.
10. Henrotin Y, Kurz B, Aigner T. Oxygen and reactive oxygen species in cartilage degradation: friends or foes? Osteoarthritis Cartilage 2005;13:643–654.
11. Abramson SB, Attur M, Amin AR, Clancy R. Nitric oxide and inflammatory mediators in the perpetuation of osteoarthritis. Curr Rheumatol Rep 2001;3:535–541.
12. Guilak F, Fermor B, Keefe FJ, et al. The role of biomechanics and inflammation in cartilage injury and repair. Clin Orthop 2004;17–26.
13. van der Kraan PM, van den Berg WB. Anabolic and destructive mediators in osteoarthritis. Curr Opin Clin Nutr Metab Care 2000;3:205–211.

CHAPTER 11

Osteoarthritis
C. Treatment

LEENA SHARMA, MD

- Nonpharmacologic treatments of osteoarthritis (OA) include education, weight management, and appropriate exercise, which may delay disease progression, reduce symptoms, and improve function.
- Nutritional supplements such as glucosamine and chondroitin sulfate have been studied in OA, may benefit some patients, and have low toxicity.
- Pharmacologic approaches to treatment include nonnarcotic analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).
- Intra-articular injection of glucocorticoids or hyaluronan may be useful for isolated joint involvement.
- Surgical joint replacement, especially at the hip and knee, can reduce pain and improve function in appropriate candidates.

It is estimated that 12% of Americans between ages 25 and 75 years have clinical signs and symptoms of osteoarthritis (OA). The increase in the prevalence of symptomatic OA with age, the inadequacy of current symptom-relieving treatments, and the lack of disease-modifying treatment each contribute to the overall burden of OA. Given the frequency of periarticular syndromes that mimic OA symptoms, it is important to establish, as much as is possible, that the given symptoms are a result of the OA itself (see Chapter 11A). The variation in responsiveness to standard treatments may be explained by the heterogeneity of OA as a clinical syndrome and the several other potential sources of pain.

Four sources of guidelines for the management of lower-limb OA include recommendations for nonpharmacological therapy and pharmacological therapy: the American College of Rheumatology (ACR; Table 11C-1) (1); the task force of the European League Against Rheumatism Standing Committee for International Clinical Studies Including Therapeutics (EULAR; Table 11C-2) (2,3); Algorithms for the Diagnosis and Management of Musculoskeletal Complaints (4); and the Institute for Clinical Systems Improvement (5). Pencharz and colleagues provide a critical appraisal of some of these sets of guidelines (6).

NONPHARMACOLOGIC THERAPY

An array of nonpharmacologic interventions for OA has been described, each in various stages of development, investigation, and application. Interventions from this burgeoning field take advantage of gains in understanding of causes of symptoms, disease progression, function loss, and disability in persons with OA. The category of nonpharmacologic therapy in OA encompasses physical activity, exercise, weight loss, education, inserts, footwear, bracing, therapeutic ultrasound, and pulsed electromagnetic field therapy. For many of these interventions, further investigation is necessary to better define their place in OA management.

For knee OA in particular, results from ongoing studies suggest that interventions targeting knee laxity, symptoms of knee instability, proprioceptive acuity, muscle function, agility, self-efficacy, and specific combinations of nonpharmacologic therapies may be especially effective and should be further developed and tested.

Some nonpharmacologic interventions for OA may ultimately be shown to contribute to secondary prevention, that is, prevention of disease progression. At present, these approaches are applied predominantly to

TABLE 11C-1. RECOMMENDATIONS (2000) FOR THE MANAGEMENT OF KNEE OSTEOARTHRITIS FROM THE AMERICAN COLLEGE OF RHEUMATOLOGY.

Nonpharmacologic therapy for patients with osteoarthritis
Patient education
Self-management programs (e.g., Arthritis Foundation Self-Management Program)
Personalized social support through telephone contact
Weight loss (if overweight)
Aerobic exercise programs
Physical therapy
Range-of-motion exercises
Muscle-strengthening exercises
Assistive devices for ambulation
Patellar taping
Appropriate footwear
Lateral-wedged insoles (for genu varum)
Bracing
Occupational therapy
Joint protection and energy conservation
Assistive devices for activities of daily living (ADL)
Pharmacologic therapy for patients with osteoarthritis
Oral
Acetaminophen
COX-2-specific inhibitor
Nonselective NSAID plus misoprostol or a proton pump inhibitor
Nonacetylated salicylate
Other pure analgesics (tramadol, opioids)
Intra-articular
Glucocorticoids
Hyaluronan
Topical
Capsaicin
Methylsalicylate

SOURCE: From Altman RD, et al. Arthritis Rheum 2000;43:1905–1915, by permission of *Arthritis and Rheumatism*.

treat symptoms and maintain or improve functioning. Many nonpharmacologic interventions are low cost, incorporate self-management approaches, and are home based, and, as such, may ultimately have substantial public health impact. Some specific suggestions are offered in Table 11C-3.

It is well documented that regular physical activity and exercise benefit symptoms, function, and quality of life, and they are crucial components of OA management. Exercise for OA should address range of motion, flexibility, aerobic conditioning, and muscle function. Muscle performance can be enhanced not only by strengthening exercise but also by functional exercise to improve muscle endurance and motor control. The daily exercise regimen—particularly exercises targeting muscle strength—should take into consideration the local joint pathology and impairments such as malalignment and laxity. In theory, exercise and activity benefits on pain and function in OA may be mediated through a variety of routes, including improvement in strength, endurance, cardiovascular fitness, and self-efficacy and reduction in excess body weight, depression, and anxiety. The reviews of Van Baar and colleagues (7) and of Baker and McAlindon (8) suggest that the effectiveness of isolated strengthening exercise is less than more comprehensive interventions that include aerobic exercise, pain modalities, and education. A small number of studies suggest that proprioceptive acuity may be improved by exercise or by orthoses as simple as a neoprene sleeve.

There is abundant epidemiologic evidence to suggest that excess body weight increases the risk of incident knee OA. Less is known about the impact of body weight on OA progression and there is a paucity of trial data concerning the discrete effects of weight reduction on OA outcomes. Nevertheless, there is a strong

TABLE 11C-2. RECOMMENDATIONS (2003) FOR THE MANAGEMENT OF KNEE OSTEOARTHRITIS FROM A TASK FORCE OF THE EULAR STANDING COMMITTEE FOR INTERNATIONAL CLINICAL STUDIES INCLUDING THERAPEUTICS (ESCISIT).

The optimal management of knee OA requires a combination of nonpharmacological and pharmacological treatment modalities.
The treatment of knee OA should be tailored according to: Knee risk factors (obesity, adverse mechanical factors, physical activity) General risk factors (age, comorbidity, polypharmacy) Level of pain intensity and disability Sign of inflammation, e.g., effusion Location and degree of structural damage
Nonpharmacological treatment of knee OA should include regular education, exercise, appliances (sticks, insoles, knee bracing), and weight reduction.
Paracetamol is the oral analgesic to try first and, if successful, the preferred long-term oral analgesic.
Topical applications (NSAID, capsaicin) have clinical efficacy and are safe.
NSAIDs should be considered in patients unresponsive to paracetamol. In patients with an increased gastrointestinal risk, nonselective NSAIDs and effective gastroprotective agents, or selective COX-2 inhibitors should be used.
SYSADOA (glucosamine sulphate, chondroitin sulphate, ASU, diacerein, hyaluronic acid) have symptomatic effects and may modify structure.
Intra-articular injection of long-acting corticosteroid is indicated for flare of knee pain, especially if accompanied by effusion.
Joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability.

SOURCE: From Jordan KM, et al. Ann Rheum Dis 2003;62:1145–1155, with permission from *Annals of the Rheumatic Diseases*.

TABLE 11C-3. SPECIFIC SUGGESTIONS FOR NONPHARMACOLOGIC INTERVENTION IN OSTEOARTHRITIS.

Address psychosocial factors
Enhance self-efficacy, using individualized approaches + arthritis self-management courses
Educate about OA
Improve coping skills
Prevent/treat anxiety and depression
Improve social support
Improve/maintain aerobic capacity, conditioning, strength, and ADL performance
Increase physical activity
Promote home exercise (aerobic + resistance)
Refer for physical and occupational therapy
Provide assistive devices
Address local factors
Adjust footwear
Refer for inserts/insoles
Promote resistance exercise cognizant of individual pathologic anatomy (i.e., physical therapy referral to learn optimal exercises for malaligned or unstable knee)
Refer for agility training
Provide weight loss program for those who are overweight

rationale that weight reduction in persons with knee OA who are overweight may delay disease progression, reduce symptoms, improve function, and lower the impact of comorbidities.

Several nutritional products are available and touted as beneficial for OA, but few have undergone rigorous testing. Among these, glucosamine and chondroitin sulfate have been evaluated in clinical trials, most of which received some manufacturer support. A meta-analysis suggested efficacy for symptoms, but also described evidence of publication bias, suggesting that the magnitude of the beneficial effect may be less than what has been reported (9). Studies of glucosamine published since the meta-analysis have had mixed results, with some trials suggesting no or very modest difference between treatment and placebo. A recent report from an National Institutes of Health–funded multicenter trial suggests that glucosamine and chondroitin (alone or in combination) were not better than placebo in reducing pain in the overall group of patients with knee OA, but that the combination may be effective in persons with moderate-to-severe knee pain (10).

There is some epidemiologic evidence that dietary intake of vitamin C and vitamin D may be associated with a reduced risk of knee OA progression and a trial of vitamin D in knee OA is ongoing. Data are insufficient at present to support a therapeutic dose of vitamins C or D for prevention or treatment of OA.

Patient education is highly recommended in the management of OA. OA patient education may have a specific focus, for example, relaxation, cognitive pain management, or exercise, or may be a multicomponent program. The Arthritis Self-Management Program (ASMP), taught by trained lay leaders at weekly sessions, includes patient education regarding disease processes, medication side effects, exercise, as well as cognitive–behavioral techniques, and a communication exercise in which participants learn to elicit support from family and friends (11). A body of literature suggests that the ASMP leads to improvement in symptoms, psychological well-being, perceived helplessness, levels of physical activity, use of cognitive pain management techniques, use of self-management behaviors such as exercise, communication with physicians, with long-term retention of initial gains. ASMP sessions are sponsored and/or organized by the national Arthritis Foundation in the United States and other organizations in Canada and the United Kingdom. A major mechanism of the beneficial effect of the ASMP is enhanced self-efficacy, a key determinant of physical functioning over time in epidemiologic studies.

Varus alignment substantially increases the likelihood of progression of subsequent medial tibiofemoral OA. For years, wedge osteotomy has been undertaken with the goal of reducing forces in the medial compartment in varus knees. Conservative approaches have also emerged. The use of a lateral wedge insole orthosis is believed to lower medial compartment load and reduce lateral tensile forces by enhancing valgus correction of the calcaneus, whether or not varus deformity at the knee is lessened. A small number of controlled trials have been reported, most of which suggest a beneficial effect on knee symptoms. Larger trials of longer duration are ongoing.

Kerrigan and colleagues found that wearing high-heeled shoes leads to a striking increase in forces across the medial and patellofemoral compartments (12). Although long-term effects of this footwear have not been elucidated, it seems prudent to minimize the wearing of high-heeled shoes.

The goal of the valgus unloading brace in medial knee OA is to produce an abduction moment to shift the joint contact force away from the stressed medial compartment. Most studies suggesting a beneficial effect on symptoms were uncontrolled or inadequately controlled. Systematic reviews suggest that there is insufficient evidence as yet to advocate either therapeutic ultrasound or pulsed electromagnetic field therapy in the management of OA.

SYSTEMIC PHARMACOLOGIC THERAPY

Pharmacologic treatment categories for OA are typically set up to designate whether drugs are symptom relieving or disease modifying. However, there is insufficient evidence as yet that any drug has a disease-modifying effect in OA.

Non-Narcotic Analgesic Medication

The most recent ACR guidelines for the medical management of OA suggest acetaminophen as an effective initial approach for mild-to-moderate pain. In keeping with this, the most recent EULAR guidelines suggest paracetamol as the initial approach as well as the best long-term choice. While some studies have shown that the effect of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) is comparable, others have revealed that NSAIDs may be more efficacious and preferred by patients. The ACR guidelines suggest NSAIDs as an alternative approach in those with moderate-to-severe pain and signs of inflammation. However, given the superior safety profile for acetaminophen, its over-the-counter availability and low cost, and concerns about the potential cardiovascular and gastrointestinal effects of NSAIDs, it seems reasonable to initiate therapy with regularly dosed acetaminophen.

Doses of acetaminophen should not exceed 4000 mg/day and the minimally effective dose should be used. As acetaminophen may increase the half-life of warfarin sodium, warfarin dosage may need to be adjusted in persons who start high dose acetaminophen. Acetaminophen-associated hepatic toxicity is rare in persons on doses used in the setting of OA but may be more likely in those with liver disease or who abuse alcohol.

Narcotic Analgesic Medication

Narcotic analgesic medication should be reserved for persons with severe OA and pain that is refractory to regularly dosed non-narcotic analgesia coupled with nonpharmacologic measures. A central goal of pain management is to provide a sufficient level of symptom improvement to allow healthy levels of physical activity and exercise that, in turn, may help to prevent function loss and disability. Given the potential negative consequences of undertreating or overtreating OA pain, the involvement of a multidisciplinary pain service should be considered, especially in the management of persons with severe OA who are ineligible for or who have opted against total joint replacement.

Nonsteroidal Anti-Inflammatory Drugs

If treatment with a non-narcotic analgesic is not effective, therapy with a nonselective NSAID or a cyclooxygenase-2 (COX-2)–selective NSAID may be initiated (see Chapter 41). NSAIDs inhibit the enzymatic activity of cyclooxygenase (COX), which is essential for the production of prostaglandins. Two isoforms of this enzyme exists, with the COX-2 isoform being most important for synthesis of prostaglandins that cause pain and inflammation. All NSAIDs inhibit COX-2, while the nonselective NSAIDs inhibit both COX-1 and COX-2. The effect of both nonselective and selective NSAIDs on symptoms may relate to their analgesic as well as their anti-inflammatory effects.

For both nonselective and COX-2–selective NSAIDs, it is recommended that a patient be started on the lowest therapeutic dose and that the dose be gradually increased until the response is satisfactory, the maximal recommended dose is reached, or the patient experiences an adverse effect. If the response is inadequate at the full dose of a given NSAID, it may be beneficial to try other NSAIDs. Efficacy does not differ substantially between nonselective and COX-2–selective NSAIDs in clinical trials. However, different NSAIDs may be more or less effective in individual patients. The use of two or more NSAIDs simultaneously does not improve efficacy but does increase the risk of toxicity. NSAIDs and acetaminophen may be used concurrently, and this combination may be more effective than using either medication alone.

Monitoring for possible occult side effects during the regular use of any NSAIDs is recommended. This should include the following: at 2 weeks or so after the institution of therapy, an examination of blood pressure, a complete blood cell count, and laboratory tests of hepatic and renal function; every 4 to 6 months, blood pressure, a complete blood cell count, hepatic and renal function tests, urinalysis, and a stool occult blood test. With routine use of NSAIDs in patients with OA, there is an increased risk of upper gastrointestinal toxicity (e.g., gastric and duodenal ulcers) and gastrointestinal bleeding, though this risk may be reduced with COX-2–selective NSAIDs. The 2000 ACR guidelines for the medical management of OA recommend either misoprostol or a proton-pump inhibitor with a nonselective NSAID in a patient at increased risk for an adverse gastrointestinal effect. Gastroprotective therapy is not felt to be necessary in those with a low risk for adverse gastrointestinal effects.

Renal toxicity (e.g., renal insufficiency, fluid retention, hyperkalemia) also occurs with all NSAIDs. Only nonselective NSAIDs are associated with disrupted platelet function, a function of COX-1 inhibition. Certain COX-2–selective NSAIDs have been associated with an increased risk for serious cardiovascular events. However, new labeling requirements are in place regarding cardiovascular effects for all NSAIDs to emphasize the possibility that all these drugs may be associated with risk. Given the toxicity issues associated with nonselective and COX-2–selective NSAIDs, it

seems most prudent to individualize this aspect of pharmacological management of OA depending upon comorbidities and individual risks.

LOCALIZED PHARMACOLOGIC THERAPY

Intra-articular administration of corticosteroids may result in pain reduction in OA joints, an effect that may be more likely in joints that show signs of inflammation. The duration of a beneficial effect may be only a few days but may last for a few months. Such therapy should not be repeated more than three times into the same joint in 1 year. A greater frequency is discouraged based predominantly on animal model data suggesting that intra-articular therapy may accelerate cartilage loss. Intra-articular steroid did not accelerate radiographic knee OA progression in one study. The effect of instilled steroid on OA progression by magnetic resonance imaging (MRI) has not been reported. Corticosteroid injection therapy should not be considered as a primary or scheduled form of therapy, but rather as an adjunct to other pharmacologic and nonpharmacologic treatment.

Intra-articular hyaluronan may result in a modest improvement in symptoms. The response appears to be slightly better in knees at earlier stages of OA. Available preparations are instilled weekly for 3 to 5 weeks. A potential adverse effect is the development of synovitis and effusion after the injection.

Topical capsaicin has some pain-relieving effect in osteoarthritic knees and hands. The best effect is associated with adherence to the recommended schedule, that is, application three to four times per day to the painful joint. Burning at the applied site diminishes with regular use. Capsaicin may be highly irritating to mucous membranes; careful hand washing after application helps to prevent mucous membrane contact.

SURGERY

Surgical options should be considered for patients with symptoms and functional loss refractory to nonsurgical pharmacologic and nonpharmacologic therapies. In patients with advanced OA coupled with severe pain and reduced function, total joint replacement is a highly effective intervention in the vast majority of patients, especially when the involved joint is the hip or the knee. Total joint replacement at other joint sites is at present less predictable than at the hip or the knee. Successful outcome hinges not only on operative factors and prevention of medical complications but on the quality of physical therapy before and after surgery. With advances in prosthetic design and fixation, the typical number of years during which loosening is very rare has increased. However, given the probable life span of most prostheses and implantation techniques, and the fact of a greater likelihood of complications with revision surgery, total joint replacement is avoided in younger individuals.

In theory, osteotomy could help to unload a stressed compartment in a malaligned knee without severe OA, and thereby prevent disease progression. However, specific indications for osteotomy in the joint with mild-to-moderate OA are not clear, and this is made more complex by the concept that removal of periarticular bone stock may make future joint replacement for that knee more complex. Recent findings suggest that arthroscopic meniscal debridement may not improve outcome in OA knees (13). Whether there are categories of meniscal pathology in OA knees that should be debrided remains to be elucidated.

REFERENCES

1. Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905–1915.
2. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidence-based approach to the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62:1145–1155.
3. Zhang W, Doherty M, Arden N, et al. EULAR evidence-based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64:669–681.
4. Algorithms for the diagnosis and management of musculoskeletal complaints. Am J Med 1997;103:3S–6S.
5. Lee JA. Adult degenerative joint disease of the knee: maximizing function and promoting joint health: Institute for Clinical System Integration. Postgrad Med 1999; 105:183–197.
6. Pencharz JN, Grigoriadis E, Jansz GF, Bombardier C. A critical appraisal of clinical practice guidelines for the treatment of lower-limb osteoarthritis. Arthritis Res 2002; 4:36–44.
7. van Baar ME, Assendelft WJJ, Dekker J, Oostendorp RAB, Bijlsma WJ. The effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee. Arthritis Rheum 1999;42:1361–1369.
8. Baker K, McAlindon T. Exercise for knee osteoarthritis. Curr Opin Rheumatol 2000;12:456–463.
9. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis; a systematic quality assessment and meta-analysis. JAMA 2000;283:1469–1475.

10. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795–808.
11. Lorig K, Holman HR. Arthritis self-management studies: a 12 year review. Health Educ Quarterly 1993;20:17–28.
12. Kerrigan DC, Todd MK, O'Riley PO. Knee osteoarthritis and high-heeled shoes. Lancet 1998;351:1399–1401.
13. Moseley JB, O'Malley K, Petersen NH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81–88.