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Osteoarthritis Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in the elderly, and its negative impact on physi cal function make it a leading cause of disability in the elderly. Because of the aging of Western populations and because obesity, a major risk factor, is increasing in prevalence, the occurrence of OA is on the rise. OA affects certain joints yet spares others (Fig. 383-1). Commonly affected joints include the hip, knee, and first metatarsal phalangeal joint (MTP) and cervical and lumbosacral spine. In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow, and ankle. Our joints were designed, in an evolutionary sense, for brachiating apes, animals that still walked on four limbs. We thus develop OA in joints that were ill designed for human tasks such as pincer grip (OA in the thumb base) and walking upright (OA in knees and hips). Some joints, like the ankles, may be spared because their articular cartilage may be uniquely resistant to loading stresses. OA can be diagnosed based on structural abnormalities or on the symptoms these abnormalities evoke. According to cadaveric studies, by elderly years, structural changes of OA are nearly universal. These include cartilage loss (seen as joint space loss on x-rays) and osteophytes. Many persons with x-ray evidence of OA have no joint symptoms, and although the prevalence of structural abnormalities is of interest in understanding disease pathogenesis, what matters more from a clinical perspective is the prevalence of symptomatic OA. Symptoms, usually joint pain, determine disability, visits to clinicians, and disease costs. Symptomatic OA of the knee (pain on most days of a recent month plus x-ray evidence of OA in that knee) occurs in ~12% of persons age ≥60 in the United States and 6% of all adults age ≥30. Symptomatic hip OA is roughly one-third as common as disease in the knee. Although radiographic hand OA and the appearance of bony enlargement in affected hand joints (Fig. 383-2) are extremely common in older Distal and proximal First carpometacarpal interphalangeal Cervical vertebrae Lower lumbar vertebrae Hip Knee First metatarsophalangeal FIGURE 383-1 Joints commonly affected by osteoarthritis.

CHAPTER 383 Osteoarthritis FIGURE 383-2 Severe osteoarthritis of the hands affecting the distal interphalangeal joints (Heberden’s nodes) and the proximal interphalangeal joints (Bouchard’s nodes). There is no clear bony enlargement of the other common site in the hands, the thumb base. persons, most affected persons have no pain. Even so, painful hand OA occurs in ~10% of elderly individuals and often produces measurable limitation in function. The prevalence of OA rises strikingly with age, being uncommon in adults aged <40 and highly prevalent in those aged >60. It is also a disease that, at least in middle-aged and elderly persons, is much more common in women than in men. X-ray evidence of OA is common in the lower back and neck, but back pain and neck pain have not been tied to findings of OA on x-ray. Thus, back pain and neck pain are

treated separately (Chaps. 18 and 19). ■ ■GLOBAL CONSIDERATIONS With the aging of the populations, both the prevalence of OA and the amount of disability worldwide related to OA have been increasing, especially in developed countries where many are living into old age. Hip OA is rare in China and in immigrants from China to the United States. Anatomic differences between Chinese and white hips may account for much of the difference in hip OA prevalence, with white hips having a higher prevalence of anatomic predispositions to the development of OA. However, OA in the knees is at least as common, if not more so, in Chinese as in whites from the United States, and knee OA represents a major cause of disability in China, especially in rural areas. DEFINITION OA is joint failure, a disease in which all structures of the joint have undergone pathologic change, often in concert. The pathologic sine qua non of disease is hyaline articular cartilage loss, present in a focal and, initially, nonuniform manner. This is accompanied by increasing thickness and sclerosis of the subchondral bony plate, by outgrowth of osteophytes at the joint margin, by stretching of the articular capsule, by variable degrees of synovitis, and by weakness of muscles bridging the joint. In knees, meniscal degeneration is part of the disease. There are numerous pathways that lead to joint failure, but the initial step is often joint injury in the setting of a failure of protective mechanisms. JOINT PROTECTIVE MECHANISMS

AND THEIR FAILURE Joint protectors include joint capsule and ligaments, muscle, sensory afferents, and underlying bone. Joint capsule and ligaments serve as joint protectors by providing a limit to excursion, thereby fixing the range of joint motion. Synovial fluid reduces friction between articulating cartilage sur faces, thereby serving as a protector against friction-induced cartilage wear. This lubrication function depends on hyaluronic acid and on lubricin, a mucinous glycoprotein secreted by synovial fibroblasts whose concentration diminishes after joint injury and in the face of synovial inflammation.

The ligaments, along with overlying skin and tendons, contain mechanoreceptor sensory nerves. These mechanoreceptors fire at different frequencies throughout a joint’s range of motion, provid ing feedback by way of the spinal cord to muscles and tendons. As a consequence, these muscles and tendons assume the right tension at appropriate points in joint excursion to act as optimal joint protectors, anticipating joint loading.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Muscles and tendons that bridge the joint are key joint protectors. Focal stress across the joint is minimized by muscle contraction that decelerates the joint before impact and assures that when joint impact arrives, it is distributed broadly across the joint surface. Failure of these joint protectors increases the risk of joint injury and OA. For example, in animals, OA develops rapidly when a sensory nerve to the joint is sectioned and joint injury induced. Similarly, in humans, Charcot’s arthropathy, a severe and rapidly progressive OA, develops when minor joint injury occurs in the presence of posterior column peripheral neuropathy. Another example of joint protector failure is rup ture of ligaments, a well-known cause of the early development of OA. ■ ■CARTILAGE AND ITS ROLE IN JOINT FAILURE A thin rim of tissue at the ends of two opposing bones, cartilage is lubri cated by synovial fluid to provide an almost frictionless surface across which these two bones move. The compressible stiffness of cartilage compared to bone provides the joint with impact-absorbing capacity. The earliest changes of OA may occur in cartilage, and abnormali ties there can accelerate disease development. The two major macro molecules in cartilage are type 2 collagen, which provides cartilage its tensile strength, and aggrecan, a proteoglycan macromolecule linked with hyaluronic

acid, which consists of highly negatively charged gly cosaminoglycans. In normal cartilage, type 2 collagen is woven tightly, constraining the aggrecan molecules in the interstices between collagen strands, forcing these highly negatively charged molecules into close proximity. The aggrecan molecule, through electrostatic repulsion of its negative charges, gives cartilage its compressive stiffness. Chondrocytes, the cells within this avascular tissue, synthesize all elements of the matrix and produce enzymes that break it down (Fig. 383-3). Cartilage matrix synthesis and catabolism are in a dynamic equilibrium influenced by the cytokine and growth factor environment. Mechanical and osmotic stress on chondrocytes induces these cells to alter gene expression and Articular cartilage Cartilage degradation Synovium Macrophage Neuropeptides Neuron Chondrocyte Mechanoflammation Apidokines Adipose tissue Osteoblast FIGURE 383-3 Selected factors involved in the osteoarthritic process including chondrocytes, bone, and synovium. Synovitis causes release of cytokines, alarmins, damage-associated molecular pattern (DAMP) molecules, and complement, which activate chondrocytes through cell-surface receptors. Chondrocytes produce matrix molecules (collagen type 2, aggrecan) and the enzymes responsible for the degradation of the matrix (e.g., ADAMTS-5 and matrix metalloproteinases [MMPs]). Bone invasion occurs through the calcified cartilage, triggered by vascular endothelial growth factor (VEGF) and other growth factors. (Reproduced with permission from De Roover A et al: Fundamentals of osteoarthritis: Inflammatory mediators in osteoarthritis. Osteoarthritis Cart 31:1303, 2023.)

increase production of inflammatory cytokines and matrix-degrading enzymes. While chondrocytes synthesize numerous enzymes, matrix metalloproteinases (MMPs; especially collagenases and ADAMTS-5) are critical enzymes in the breakdown of cartilage matrix. Local inflammation accelerates the development and progression of osteoarthritis and increases the likelihood that an osteoarthritic joint will be painful. Some of this inflammation may be induced by mechan ical stimuli, so called mechanoinflammation. The synovium, carti lage, and bone all influence disease development through cytokines, chemokines, and even complement activation (Fig. 383-3). Matrix fragments released from cartilage stimulate synovium, which releases inflammatory cytokines, and they, in turn, induce chondrocytes to synthesize other proinflammatory molecules. Ultimately, the combina tion of effects on chondrocytes triggers matrix degradation. Growth factors are also part of this complex network, with bone morphogenetic protein 2 (BMP-2) and transforming growth factor β (TGF-β) playing prominent roles in stimulating the development of osteophytes. Trig gered by local vascular endothelial growth factor (VEGF) synthesis, blood vessels invade cartilage and, with them, come nerves that may bring nociceptive innervation. With aging, articular chondrocytes develop a senescence-associated secretory phenotype, exhibiting a decline in synthetic capacity and pro ducing proinflammatory mediators and matrix-degrading enzymes. These chondrocytes are unable to maintain tissue homeostasis (such as after insults of a mechanical or inflammatory nature). Thus, with age, cartilage is easily damaged by minor sometimes unnoticed injuries, including those that are part of daily activities. OA cartilage is characterized by gradual depletion of aggrecan, an unfurling of the tightly woven collagen matrix, and loss of type 2 col lagen. With these changes comes increasing vulnerability of cartilage, which loses its compressive stiffness. RISK FACTORS Risk factors for OA can be understood in terms of their effect either on joint vulnerability or joint loading. On the one hand, a vulnerable joint whose protectors are dysfunctional can develop OA with minimal lev els of loading, perhaps even levels encountered during everyday activi ties. On the other hand, in a young joint with competent protectors, a DAMPs Cytokines Synoviocyte Osteophyte Growth factors Subchondral bone Activated osteoblast

Intrinsic joint vulnerabilities (local environment) Previous damage (e.g., meniscectomy) Bridging muscle weakness Increasing bone density Malalignment Proprioceptive deficiences Systemic factors affecting joint vulnerability Use (loading) factors acting on joints Increased age Female gender Racial/ethnic factors Genetic susceptibility Nutritional factors Obesity Injurious physical activities Susceptibility to OA Osteoarthritis or its progression FIGURE 383-4 Risk factors for osteoarthritis (OA) either contribute to the susceptibility of the joint (systemic factors or factors in the local joint environment) or increase risk by the load they put on the joint. Usually, a combination of loading and susceptibility factors is required to cause disease or its progression. major acute injury or long-term overloading is necessary to precipitate disease (Fig. 383-4). ■ ■SYSTEMIC RISK FACTORS THAT AFFECT

JOINT VULNERABILITY Age is the most potent risk factor for OA. Radiographic evidence of OA is rare in individuals aged <40; however, in some joints, such as the hands, OA occurs in >50% of persons aged >70. Aging increases joint vulnerability through several mechanisms. Whereas dynamic loading of joints stimulates matrix synthesis by chondrocytes in young cartilage, aged cartilage is less responsive to these stimuli. As a conse quence of this failure to synthesize matrix with loading, cartilage thins with age, and thinner cartilage experiences higher shear stress and is at greater risk of damage. Also, joint protectors fail more often with age. Muscles that bridge the joint become weaker with age and respond less quickly to oncoming impulses. Sensory nerve input slows with age, retarding the feedback loop of mechanoreceptors to muscles and tendons related to their tension and position. Ligaments stretch with age, making them less able to absorb impulses. These factors work in concert to increase the vulnerability of older joints to OA. Older women are at high risk of OA in all joints, a risk that increases as women reach their sixth decade. Although hormone loss with meno pause may contribute to this risk, there is little understanding of the unique vulnerability of older women versus men. ■ ■HERITABILITY AND GENETICS AND THEIR RELATION TO JOINT VULNERABILITY OA is a heritable disease, but its heritability is mostly joint specific. Nearly 60–65% of OA in hips or hands may be attributed to shared genetics within a family. However, heritability of knee OA is, at most, 30%, with some studies suggesting no heritability at all. Knees are susceptible to nongenetic factors like activities that affect joint loading and risk of injury. On the other hand, many people with OA develop “generalized OA” or multisite OA, but the involvement of multiple joints with OA is usually a consequence of aging rather than genetics. The best replicated genetic variant known to increase OA risk lies in the locus for growth differentiation factor 5 (GDF5). It affects epigen etic regulation of GDF5 activity, resulting in reduction in GDF5 expres sion. GDF5 probably affects joint shape, a mechanism by which genes increase disease risk. Minor abnormalities in joint shape can make a joint vulnerable to damage if focal stresses across the joint increase.

■ ■RISK FACTORS IN THE JOINT ENVIRONMENT Some risk factors increase vulnerability of the joint through local effects on the joint environment. With changes in joint anatomy, for example, load across the joint is no longer distributed evenly across the joint surface, but rather shows an increase in focal stress. In the hip, three uncommon developmental abnormalities occurring in utero or in childhood—congenital dysplasia, Legg-Perthes disease, and slipped capital femoral epiphysis—leave a child with distortions of hip joint anatomy that often lead to OA later in life. Girls are predominantly affected by acetabular dysplasia, a mild form of congenital dysplasia, whereas the other abnormalities more often affect boys. Depending on the severity of the anatomic abnormalities, hip OA occurs either in young adulthood (severe abnormalities) or middle age (mild

abnormalities). Femoroacetabular impingement can develop during adolescence. It is a clinical syndrome in which an outgrowth of bone at the femur's head/neck junction thought to develop during closure of the growth plate results in abnormal contact between the femur and acetabulum, especially during hip flexion and rotation. This leads to cartilage and labral damage, to hip pain, and ultimately in later life, to an increased risk of hip OA.

CHAPTER 383 Osteoarthritis Major injuries to a joint also can produce anatomic abnormalities that leave the joint susceptible to OA. For example, a fracture through the joint surface often causes OA in joints in which the disease is oth erwise rare such as the ankle and the wrist. Avascular necrosis can lead to collapse of dead bone at the articular surface, producing anatomic irregularities and subsequent OA. Tears of ligamentous and fibrocartilaginous structures that protect the joints, such as the anterior cruciate ligament or meniscus in the knee and the labrum in the hip, can lead to premature OA. Meniscal tears increase with age and, when chronic, are often asymptomatic but lead to adjacent cartilage damage and accelerated OA. Even recalled injuries in which the affected person never received a diagnosis may increase risk of OA. For example, in the Framingham Study subjects, men with a history of major knee injury, but no surgery, had a 3.5-fold increased risk for subsequent knee OA. Another source of anatomic abnormality is malalignment across the joint (Fig. 383-5), a factor best studied in the knee. Varus (bow legged) knees with OA are at exceedingly high risk of cartilage loss in the medial or inner compartment of the knee, whereas valgus (knockkneed) malalignment predisposes to rapid cartilage loss in the lateral compartment. Malalignment causes this effect by increasing stress on a focal area of cartilage, which then breaks down; it also causes dam age to bone underlying the cartilage, producing bone marrow lesions seen on magnetic resonance imaging (MRI). Malalignment in the knee often produces such a substantial increase in focal stress within the knee (as evidenced by its destructive effects on subchondral bone) that severely malaligned knees may be destined to progress regardless of the status of other risk factors. Weakness in the quadriceps muscles bridging the knee increases the risk of the development of painful OA in the knee, especially in women. Normal Varus Knock knees (valgus) FIGURE 383-5 The two types of limb malalignment in the frontal plane: varus, in which the stress is placed across the medial compartment of the knee joint, and valgus, which places excess stress across the lateral compartment of the knee.

High bone density also increases OA risk, especially risk of a subtype of OA characterized by large osteophytes.

■ ■LOADING FACTORS Obesity Three to six times body weight is transmitted across the knee during single-leg stance. Any increase in weight may be multiplied by this factor to reveal the excess force across the knee in overweight per sons during walking. Obesity is a potent risk factor for the development of knee OA and, less so, for hip OA. It is a stronger risk factor for disease in women than in men, and for women, the relationship of weight to the risk of disease is linear, so that with each pound increase in weight, there is a commensurate increase in risk. Not only is obesity a risk factor for OA in weight-bearing joints, but obese persons have more pain from the disease. Weight loss greater than 10% of body weight reduces cartilage loss and, in most affected persons, alleviates pain. PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Obesity's effect on the development and progression of disease, especially in knees, is mediated mostly through the increased loading in weight-bearing joints that occurs in overweight persons. However, high levels of leptin, an adipokine, are associated with increasing pain severity in OA

regardless of the joint affected. Repeated Use of Joint and Exercise There are two categories of repetitive joint use: occupational use and leisure time physical activities. Workers who, over many years, perform repetitive tasks as part of their occupations are at high risk of developing OA in joints they use repeatedly. Workers whose jobs require regular knee bending or lifting or carrying heavy loads have a high rate of knee OA. One reason why workers may get disease is that during long days at work, their muscles may gradually become exhausted, no longer serving as effective joint protectors. It is widely recommended for people to adopt an exercise-filled life style, and long-term studies of exercise suggest no consistent associa tion of exercise with OA risk in most persons. However, persons who already have injured joints may put themselves at greater risk by engag ing in certain types of exercise. For example, persons who have already sustained major knee injuries are at increased risk of progressive knee OA as a consequence of running. In addition, compared to nonrun ners, elite runners (professional runners and those on Olympic teams) have high risks of both knee and hip OA. Lastly, although recreational runners are not at increased risk of knee OA, studies suggest that they have a modest increased risk of disease in the hip. PATHOLOGY The pathology of OA provides evidence of the involvement of many joint structures in disease. Cartilage initially shows surface fibrillation and irregularity. As disease progresses, focal erosions develop there, and these eventually extend to the subjacent bone. With further pro gression, cartilage erosion down to bone expands to involve a larger proportion of the joint surface, even though OA remains a focal disease with nonuniform loss of cartilage. After an injury to cartilage, chondrocytes undergo mitosis and clus tering. Although the metabolic activity of these chondrocyte clusters is high, the net effect of this activity is to promote proteoglycan depletion in the matrix surrounding the chondrocytes. This is because the catabolic activity is greater than the synthetic activity. As disease develops, colla gen matrix becomes damaged, the negative charges of proteoglycans get exposed, and cartilage swells from ionic attraction to water molecules. Because in damaged cartilage proteoglycans are no longer forced into close proximity, cartilage does not bounce back after loading as it did when healthy, and cartilage becomes vulnerable to further injury. With loss of cartilage comes alteration in subchondral bone. Stimu lated by growth factors and cytokines, osteoclasts and osteoblasts in the bony plate just underneath cartilage become activated. Bone forma tion produces a thickening of the subchondral plate that occurs even before cartilage ulcerates. Trauma to bone during joint loading may be the primary factor driving this bone response, with healing from injury (including microcracks) inducing remodeling. Small areas of osteonecrosis usually exist in joints with advanced disease. Bone death may also be caused by bone trauma with shearing of microvasculature, leading to a cutoff of vascular supply to some bone areas.

At the margin of the joint, near areas of cartilage loss, osteophytes form. These start as outgrowths of new cartilage, and with neurovas cular invasion from the bone, this cartilage ossifies. Osteophytes are an important radiographic hallmark of OA. The synovium produces lubricating fluids that minimize shear stress during motion. In healthy joints, the synovium consists of a single dis continuous layer filled with fat and containing two types of cells, macro phages and fibroblasts, but in OA, it can sometimes become edematous and inflamed. There is a migration of macrophages from the periphery into the tissue, and cells lining the synovium proliferate. Inflammatory cytokines and alarmins secreted by the synovium activate chondrocytes to produce enzymes that accelerate destruction of matrix. Additional pathologic changes occur in the capsule, which stretches, becomes edematous, and can become fibrotic. The pathology of OA is not identical across joints. In hand joints with severe OA, for example, there are often cartilage erosions in the center of the joint

probably produced by bony pressure from the oppo site side of the joint. Basic calcium phosphate and calcium pyrophosphate dihydrate crystals are present microscopically in most joints with end-stage OA. Their role in osteoarthritic cartilage is unclear, but their release from cartilage into the joint space and joint fluid likely triggers synovial inflammation, which can, in turn, produce release of cytokines and trigger nociceptive stimulation. SOURCES OF PAIN Because healthy cartilage is aneural, cartilage loss alone is not accom panied by much pain. Thus, pain in OA likely arises from structures outside the cartilage. Innervated structures in the joint include the synovium, ligaments, joint capsule, muscles, and subchondral bone. Most of these are not visualized by x-ray, and the severity of x-ray changes in OA correlates poorly with pain severity. However, in later stages of OA, loss of cartilage integrity accompanied by neurovascular invasion may contribute more to pain. Based on MRI studies in osteoarthritic knees comparing those with and without pain and on studies mapping tenderness in unanesthetized joints, likely sources of pain include synovial inflammation, joint effu sions, and bone marrow edema. Modest synovitis develops in many but not all osteoarthritic joints. The presence of synovitis on MRI is cor related with the presence and severity of knee pain, and potentially with pain sensitization. Capsular stretching from fluid in the joint stimulates nociceptive fibers there, inducing pain. Increased focal loading as part of the disease not only damages cartilage but probably also injures the underlying bone. As a consequence, bone marrow edema appears on the MRI; histologically, this edema signals the presence of microcracks and scar, which are the consequences of trauma. These lesions may stimu late bone nociceptive fibers. Pain may arise from outside the joint also, including bursae near the joints. Common sources of pain near the knee are anserine bursitis and iliotibial band syndrome. Much of the pain experienced in OA occurs when nociceptors in the joint are stimulated during weight-bearing activities. However, the pain may eventually become more constant and present at rest, and this suggests other mechanisms contribute to the pain experience. The pathologic changes of OA may lead to alterations in nervous system signaling (Chap. 18). Specifically, peripheral nociceptors can become more responsive to sensory input, known as peripheral sensitization, and there can also be an increase in facilitated central ascending noci ceptive signaling, known as central sensitization. Individuals with OA may also have insufficient descending inhibitory modulation. Some individuals may be genetically predisposed to becoming sensitized; however, regardless of the etiology, these nervous system alterations are associated with more severe pain, contribute to the presence of allodynia and hyperalgesia in patients with OA, and may predispose to development of chronic pain. CLINICAL FEATURES Joint pain from OA is primarily activity-related in the early stages of the disease. Pain comes on either during or just after joint use and then gradually resolves. Examples include knee or hip pain with going up or

FIGURE 383-6 X-ray and magnetic resonance imaging (MRI) of knee with medial osteoarthritis. X-ray shows osteophytes at the medial and lateral tibia and femur and joint space narrowing of the medial tibiofemoral joint. Coronal intermediate-weighted fat-suppressed MRI confirms the presence of medial and lateral osteophytes and the medial tibiofemoral joint space narrowing. There is diffuse denuded area with no cartilage remaining at the weight-bearing medial tibiofemoral joint (arrows). There is also a severe medial meniscus extrusion (arrowhead). Bone marrow lesions, which provide evidence of bone injury, are present at medial tibia, medial femur, and intraspinous tibial region. Cartilage focal defects are also seen at the lateral weight-bearing femur and tibia.

down stairs, pain in weight-bearing joints when walking, and, for hand OA, pain when cooking. Early in disease, pain is episodic, triggered often by overactive use of a diseased joint, such as a person with knee OA taking a long run and noticing a few days of pain thereafter. As disease progresses,

the pain becomes continuous and even begins to be bothersome at night. Stiffness of the affected joint may be prominent, but morning stiffness is usually brief (<30 min). In knees, buckling may occur, in part, from weakness of muscles crossing the joint. Mechanical symptoms, such as buckling, catching, or locking, could also signify internal derangement, like an anterior cruciate ligament or meniscal tear; however, these symptoms, which are common in persons with knee OA, need to be further evaluated only if they develop after an acute knee injury. In the knee, pain with activities requiring knee flexion, such as stair climbing and arising from a chair, often emanates from the patellofemoral compartment of the knee, which does not actively articulate until the knee is bent ~35°. OA is the most common cause of chronic knee pain in persons aged

> 45, but the differential diagnosis is long. Inflammatory arthritis is likely if there is prolonged morning stiffness, and many other joints are affected. Bursitis occurs commonly around knees and hips. A physical examination should focus on whether tenderness is over the joint line (at the junction of the two bones around which the joint is articulat ing) or outside of it. Anserine bursitis, medial and distal to the knee, is an extremely common cause of chronic knee pain that may respond to a glucocorticoid injection. Prominent nocturnal pain in the absence of end-stage OA merits a distinct workup. For hip pain, OA can be detected by loss of internal rotation on passive movement, and pain isolated to an area lateral to the hip joint usually reflects the presence of trochanteric bursitis. No blood tests are routinely indicated for workup of patients with OA unless symptoms and signs suggest inflammatory arthritis. Exami nation of the synovial fluid is often more helpful diagnostically than

CHAPTER 383 Osteoarthritis an x-ray. If the synovial fluid white count is >1000/μL, inflammatory arthritis or gout or pseudogout is likely, the latter two being also identi fied by the presence of crystals. Radiographs are not indicated in the workup of OA. They should be ordered only when joint pain and physical findings are not typical of OA or if pain persists after inauguration of treatment effective for OA. In OA, imaging findings (Fig. 383-6) correlate poorly with the pres ence and severity of pain. Further, in both knees and hips, radiographs may be normal in early disease as they are insensitive to cartilage loss and other early findings. Although MRI may reveal the extent of pathology in an osteo arthritic joint, it is not indicated as part of the diagnostic workup. Findings such as meniscal tears and cartilage and bone lesions occur not only in most patients with OA in the knee but also in most older persons without joint pain. MRI findings rarely warrant a change in therapy. TREATMENT Osteoarthritis The goals of the treatment of OA are to alleviate pain and minimize loss of physical function. To the extent that pain and loss of function are consequences of inflammation, of weakness across the joint, and of laxity and instability, the treatment of OA involves addressing each of these impairments. Comprehensive therapy consists of a multimodality approach including physical modalities and phar macologic elements. Foundational to OA management is patient education and self-management strategies. Patients with mild and intermit tent symptoms may need only symptomatic management and/ or treatments aimed at weight loss, physical activity, exercise, and

self-management strategies. Patients with ongoing, disabling pain are likely to need both physical modalities and pharmacotherapy.

Treatments for knee OA have been more completely evaluated than those for hip and hand OA or for disease in other joints. Thus, although the principles of treatment are identical for OA in all joints, we shall focus below on the treatment of knee OA, not ing specific recommendations for disease in other joints, especially when they differ from those for the knee. PHYSICAL MANAGEMENT MODALITIES Because OA is a mechanically driven disease, the mainstay of treat ment involves altering loading across the painful joint and improv ing the function of joint protectors, so they can better distribute load across the joint. Ways of lessening focal load across the joint include: PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders

1. Avoiding painful activities as these are usually activities that overload the joint
2. Improving the strength and conditioning of muscles that bridge the joint to optimize their function
3. Unloading the joint, either by redistributing load within the joint with a brace or a splint or by unloading the joint during weight bearing with a cane or a crutch The simplest treatment for many patients is to avoid activities that precipitate pain. For example, for the middle-aged patient whose long-distance running brings on symptoms of knee OA, a less demanding form of weight-bearing activity may alleviate all symptoms. For an older person whose daily walks up and down hills bring on knee pain, routing these away from hills might elimi nate symptoms. Weight loss is a central strategy for those who are overweight or obese, particularly for knee OA. Each pound of weight loss has a multiplier effect, unloading both knees and hips and probably relieving pain in those joints. Depending on how much weight loss occurs, bariatric surgery and drugs that cause weight loss such as glucagon-like peptide 1 receptor agonists (GLP1R agonists) often reduce pain and may slow structural disease progression. In hand joints affected by OA, splinting, by limiting motion, often minimizes pain for patients with involvement especially in the base of the thumb. Weight-bearing joints such as knees and hips can be unloaded by using a cane in the hand opposite the affected joint for partial weight bearing. A physical therapist can help teach the patient how to use the cane optimally, including ensuring that its height is optimal for unloading. Crutches or walkers can serve a similar beneficial function. Exercise Osteoarthritic pain in knees or hips during weight bear ing results in lack of activity and poor mobility, and because OA is so common, the inactivity that results increases the risk of cardio vascular disease and obesity. Aerobic capacity is poor in most elders with symptomatic knee OA, worse than others of the same age. Weakness in muscles that bridge osteoarthritic joints is multi factorial in etiology. First, there is a decline in strength with age. Second, with limited mobility comes disuse muscle atrophy. Third, patients with painful knee or hip OA alter their gait to lessen load ing across the affected joint, and this further diminishes muscle use. Fourth, “arthrogenous inhibition” may occur, whereby contrac tion of muscles bridging the joint is inhibited by a nerve afferent feedback loop emanating in a swollen and stretched joint capsule; this prevents attainment of voluntary maximal strength. Because adequate muscle strength and conditioning are critical to joint pro tection, weakness in a muscle that bridges a diseased joint makes the joint more susceptible to further damage and pain. The degree of weakness correlates strongly with the severity of joint pain and the degree of physical

limitation. One of the cardinal elements of the treatment of OA is to improve the functioning of muscles sur rounding the joint. Trials in knee and hip OA have shown that exercise lessens pain and improves physical function. Most effective exercise regimens consist of aerobic and/or resistance training, the latter of which

focuses on strengthening muscles across the joint. Treatment guide lines strongly recommend exercise for knee and hip OA with no hierarchy regarding type of exercise due to lack of sufficient headto-head data. Exercises are likely to be effective especially if they train muscles for the activities a person performs daily. Activities that increase pain in the joint should be avoided. Range-of-motion exercises, which do not strengthen muscles, and isometric exer cises that strengthen muscles, but not through range of motion, are unlikely to be effective by themselves. Low-impact exercises, including water aerobics and water resistance training, are often better tolerated by patients than exercises involving impact load ing, such as running or treadmill exercises. Evidence suggests that high-intensity strengthening is no more effective in reducing knee pain than less aggressive strengthening regimens. The exercise regimen needs to be individualized to optimize effectiveness, and patients should be referred to an exercise class or a therapist who can create an individualized regimen. In addition to conventional exercise regimens, tai chi may be effective for knee OA. However, there is no strong evidence that patients with hand OA benefit from therapeutic exercise. Adherence over the long term is the major challenge to an exer cise prescription. In trials involving patients with knee OA who were engaged in exercise treatment, from a third to over half of patients stopped exercising by 6 months. Less than 50% continued regular exercise at 1 year. The strongest predictor of a patient’s con tinued exercise is a previous personal history of successful exercise. Physicians should reinforce the exercise prescription at each clinic visit, help the patient recognize barriers to ongoing exercise, and identify convenient times for exercise to be done routinely. Mobile health and wearable technologies are increasingly being used to encourage adherence to exercise. The combination of exercise with calorie restriction and weight loss is especially effective in lessening pain. Correction of Malalignment Malalignment in the frontal plane (varus-valgus) markedly increases the stress across the joint, which can lead to progression of disease and to pain and disability (Fig. 383-5). Correcting varus-valgus malalignment, either surgically or with bracing, may relieve pain in persons whose knees are malaligned. However, correcting malalignment is often challenging. Fitted braces that straighten varus knees by putting valgus stress across the knee can be effective. Unfortunately, many patients are unwilling to wear a realigning knee brace; in addition, in patients with obese legs, braces may slip with usage and lose their realigning effect. Braces are indicated for willing patients who can learn to put them on correctly and on whom they do not slip. Shoes modified with rubber hemispheres on the sole that alter alignment of the proximal knee have shown efficacy in trials especially if worn for brief periods daily over several months. Pain from the patellofemoral compartment of the knee can be caused by tilting of the patella or patellar malalignment with the patella riding laterally in the femoral trochlear groove. Using a patel lar brace to realign the patella, or tape to pull the patella back into the trochlear sulcus or reduce its tilt, can lessen patellofemoral pain. However, patients may find it difficult to apply tape, with skin irrita tion common, and, like realigning braces, patellar braces may slip. Although their effect on malalignment is questionable, neoprene sleeves pulled up to cover the knee lessen pain and are easy to use and popular among patients. The explanation for their therapeutic effect on pain is unclear. In patients with knee OA, acupuncture produces modest pain relief compared to placebo needles and may be an adjunctive treat ment, though placebo effect is likely high. In patients with

refrac tory joint pain from OA, radiofrequency ablation of the nerves innervating the joint has been shown to provide prolonged pain relief, although long-term safety is unknown. PHARMACOTHERAPY Although approaches involving physical modalities constitute its mainstay, pharmacotherapy serves an important adjunctive role

in OA treatment for symptom management. Available drugs are administered using oral, topical, and intraarticular routes. To date, there are no available drugs that alter the disease process itself. Acetaminophen, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and Cyclooxygenase-2 (COX-2) Inhibitors The treatment effect of acetaminophen (paracetamol) in OA is small and not considered clinically meaningful (Table 383-1). However, for a minority of patients, it is adequate to control symptoms, in which case more toxic drugs such as oral NSAIDs can be avoided. NSAIDs are the most popular drugs to treat osteoarthritic pain. They can be administered either topically or orally. In clinical trials, oral NSAIDs produce ~30% greater improvement in pain than high-dose acetaminophen. Response to NSAIDs varies greatly across patients. Occasional patients treated with NSAIDs experience dramatic pain relief, whereas others experience little improvement. Initially, NSAIDs should be administered topically or taken orally on an “as-needed” basis because side effects are less frequent with low intermittent doses. For those with mild symp toms, topical NSAIDs may be sufficient to reduce pain. If topicals or occasional oral medication use is insufficiently effective, then daily treatment may be indicated, with an anti-inflammatory dose selected (Table 383-1). Topical NSAIDs absorbed through the skin have plasma concen trations an order of magnitude lower than the same amount of drug administered orally. However, when these drugs are administered TABLE 383-1 Pharmacologic Treatment for Osteoarthritis MAXIMAL DOSAGE COMMENTS TREATMENT Take with food. Increased risk of myocardial infarction and stroke for some NSAIDs. High rates of gastrointestinal side effects, including ulcers and bleeding. Patients at high risk for gastrointestinal side effects should also take either a proton pump inhibitor or misoprostol.a There is an increase in gastrointestinal side effects or bleeding when taken with acetylsalicylic acid. Can also cause edema and renal insufficiency. Oral NSAIDs and COX-2 inhibitors Naproxen Salsalate Ibuprofen Celecoxib 375–500 mg bid 1500 mg bid 600–800 mg qid/tid 100–200 mg qd Acetaminophen Up to 2 g/d Of limited efficacy; conditionally recommended. Opiates Common side effects include dizziness, sedation, nausea, vomiting, dry mouth, constipation, urinary retention, and pruritus. Addiction risk. Less efficacious than oral NSAIDs. Topical NSAIDs Rub onto hands/knees. Few systemic side effects. Diclofenac Na 1% gel 4 g qid Skin irritation common. Capsaicin 0.025–0.075% cream tid/qid Can irritate mucous membranes. Intraarticular injections Steroids Various Hyaluronans Varies from 3 to 5 weekly injections Mild to moderate pain at injection site. Controversy exists regarding efficacy. aPatients at high risk include those with previous gastrointestinal events, persons ≥60 years, and persons taking glucocorticoids. Trials have shown the efficacy of proton pump inhibitors and misoprostol in the prevention of ulcers and bleeding. Misoprostol is associated with a high rate of diarrhea and cramping; therefore, proton pump inhibitors are more widely used to reduce NSAID-related gastrointestinal symptoms. Abbreviations: COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs. Source: From DT Felson: Osteoarthritis of the Knee. N Engl J Med 354:841, 2006.

topically over a superficial joint (knees, hands, but not hips), the drug can be found in joint tissues such as the synovium and car tilage. Generally, topical NSAIDs are slightly less efficacious than oral agents, but have far fewer gastrointestinal (GI) and systemic side effects. Topical NSAIDs often

cause local skin irritation where the medication is applied, inducing redness, burning, or itching (see Table 383-1).

CHAPTER 383 Oral NSAIDs are often effective in reducing moderate or severe joint pain, but they have substantial and frequent side effects, the most common of which is upper GI toxicity, including dyspepsia, nausea, bloating, GI bleeding, and ulcer disease. Certain oral agents including celecoxib and nabumetone are safer to the stomach than others. Major NSAID-related GI side effects can occur in patients who do not complain of upper GI symptoms. Patients should be reminded to take low-dose aspirin and ibuprofen or naproxen at different times during the day to avoid a drug interaction. Osteoarthritis Because of the increased rates of cardiovascular events associated with conventional NSAIDs such as diclofenac, many of these drugs are not appropriate long-term treatment choices for older persons with OA, especially those at high risk of heart disease or stroke. The American Heart Association has identified COX-2 inhibitors as putting patients at high risk, although low doses of celecoxib (≤200 mg/d) are not associated with an elevation of risk. Naproxen is a safe NSAID from a cardiovascular perspective, but it does have GI toxicity. There are other common side effects of NSAIDs, including the tendency to develop edema because of prostaglandin inhibition of afferent blood supply to glomeruli in the kidneys and, for similar reasons, a predilection toward reversible renal insufficiency. Blood pressure may increase modestly in some NSAID-treated patients. Oral NSAIDs should not be used in patients with stage 3, 4, or 5 renal disease. Intraarticular Injections: Glucocorticoids, Hyaluronic Acid, and Other Products Because synovial inflammation is likely to be a major cause of pain in patients with OA, local anti-inflammatory treatments administered intraarticularly may be effective in ame liorating pain for up to 3 months. Glucocorticoid injections provide such efficacy, but response is variable, with some patients having little relief of pain, whereas most experience pain relief lasting up to several months. Synovitis, a major cause of joint pain in OA, may abate after an injection, and this correlates with the reduction in knee pain severity. Glucocorticoid injections are useful to get patients over acute flares of pain. Repeated injections may cause minor amounts of cartilage loss, but these do not appear to increase risk of disease progression, worsening pain, functional limitations, or the need for surgery. Hyaluronic acid injections can be given for treatment of symp toms in knee and hip OA, but most evidence suggests they have little efficacy versus placebo (Table 383-1). Few rigorous studies of intraarticular stem cell therapy and platelet-rich plasma (PRP) have been conducted to date. Further, the composition of the injected biologic materials reflecting stem cells or PRP has not been standardized, making it challenging to compare across studies due to variability in formulation. Other Classes of Drugs and Nutraceuticals Opioids have only modest short-term efficacy in treating pain in hip or knee OA without evidence of long-term benefit and, given concerns about opioid dependency, should be avoided. If NSAIDs are ineffective, one option is the use of duloxetine, which is U.S. Food and Drug Administration approved for OA. Duloxetine may be particularly efficacious when knee pain is part of a syndrome of widespread pain. Biologic agents and disease-modifying agents used for rheuma toid arthritis have been tested for OA, but trials have mostly been negative. Notable exceptions are two randomized trials for hand OA, one of 6 weeks of prednisolone and the other of 6 months of methotrexate. Both trials demonstrated reductions in hand pain compared with placebo. In a large randomized trial, GLP1R ago nists reduced knee pain in obese patients.

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