Chapter 3
Osteoarthritis

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Take-Home Points

- OA is a systemic (low-level) inflammatory disease characterized by the destruction of articular cartilage, subchondral bone changes, joint pain, and loss of joint function.
- Several factors contribute to the development of OA, including genetic and epigenetic risk, advanced age, obesity, and preceding trauma.
- OA is the leading cause of chronic disability in the USA.
- OA is diagnosed clinically; radiographs and synovial fluid analysis is generally not indicated for the diagnosis.
- The cornerstone of OA treatment involves physical therapy and exercise.
- Pharmacologic therapy for OA should focus on the use of nonsteroidal anti-inflammatory drugs (NSAIDs), either systemic or topical, and intra-articular glucocorticoids in patients with low risk. Alternative treatments, including duloxetine, may be beneficial. There have been no dietary or supplement interventions definitively shown to improve the pain or physical function of OA patients.
- Surgical therapy (arthroplasty) offers substantial relief of pain, above and beyond what is seen with pharmacologic treatment, for OA sufferers, although a portion of patients may experience persistent symptoms.

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Introduction

Osteoarthritis (OA) is a chronic, debilitating musculoskeletal disease characterized by progressive loss of joint function leading to pain, mobility loss, and increased morbidity. It is the leading cause of chronic disability in the USA and affects roughly 23% of all adults, rising to 49.7% of those over 65 years of age [1], and is the most rapidly growing major health condition worldwide [2]. A variety of factors including age, obesity, genetics, mechanical trauma, and inflammation all contribute to the development and progression of OA [3], although patients develop OA at different rates. Especially in early disease, pain and functional limitation are not strongly correlated with severity radiographic joint space loss. Early diagnosis and prediction of those patients who will go on to have rapidly progressive disease remains a challenge and is a topic of intensive biomarker research.

The osteoarthritic joint is characterized by cartilage degradation without an appropriate healing response, sclerosis of underlying subchondral bone, and synovial inflammation [4]. Although many genetic association studies have been performed, a strong genetic component, particularly for knee and hip OA, has yet to be identified. Only a handful of genetic susceptibility loci have been confirmed, all with relatively mild disease contribution (hazard ratios of <2) [5]. Several studies have suggested that age-related changes to epigenetic processes may be a potential cause of late onset human diseases such as osteoarthritis, and recent reports have demonstrated an association between epigenetic changes and the development and progression of knee and hip OA [6].

There have been to date no disease-modifying (cartilage-repairing) drugs approved for the treatment of OA. Management consists of a multimodal therapeutic approach including weight loss, physical therapy, pain-relieving drugs such as nonsteroidal anti-inflammatories (NSAIDs), and intra-articular drugs. The "definitive" treatment for most patients with knee and hip OA remains joint replacement, which offers substantial relief in pain and improvement in physical function in the majority.

In this chapter, we will delve more deeply into this most common of rheumatic diseases, including a discussion of our most up-to-date understanding of the underlying pathophysiology of OA, risk factors for OA development, the clinical presentation and diagnosis of OA, and treatment strategies for OA.

Pathophysiology

The traditional dogma of OA pathogenesis was that it resulted from "wear and tear"; that is, chronic overloading of weight-bearing joints slowly wears away articular cartilage surfaces, leading to eventual failure of the joint. Over the past decades, researchers have come to realize that OA is a much more complex disease than this simplified explanation would suggest. Indeed, a variety of factors, including systemic inflammation (particularly, as we will discuss, the innate immune system), genetic risk, epigenetic responses to local environmental factors and age, and biomechanical changes all contribute to the development of OA, itself a whole-joint (perhaps even whole-body) disease (Fig. 3.1, Table 3.1).

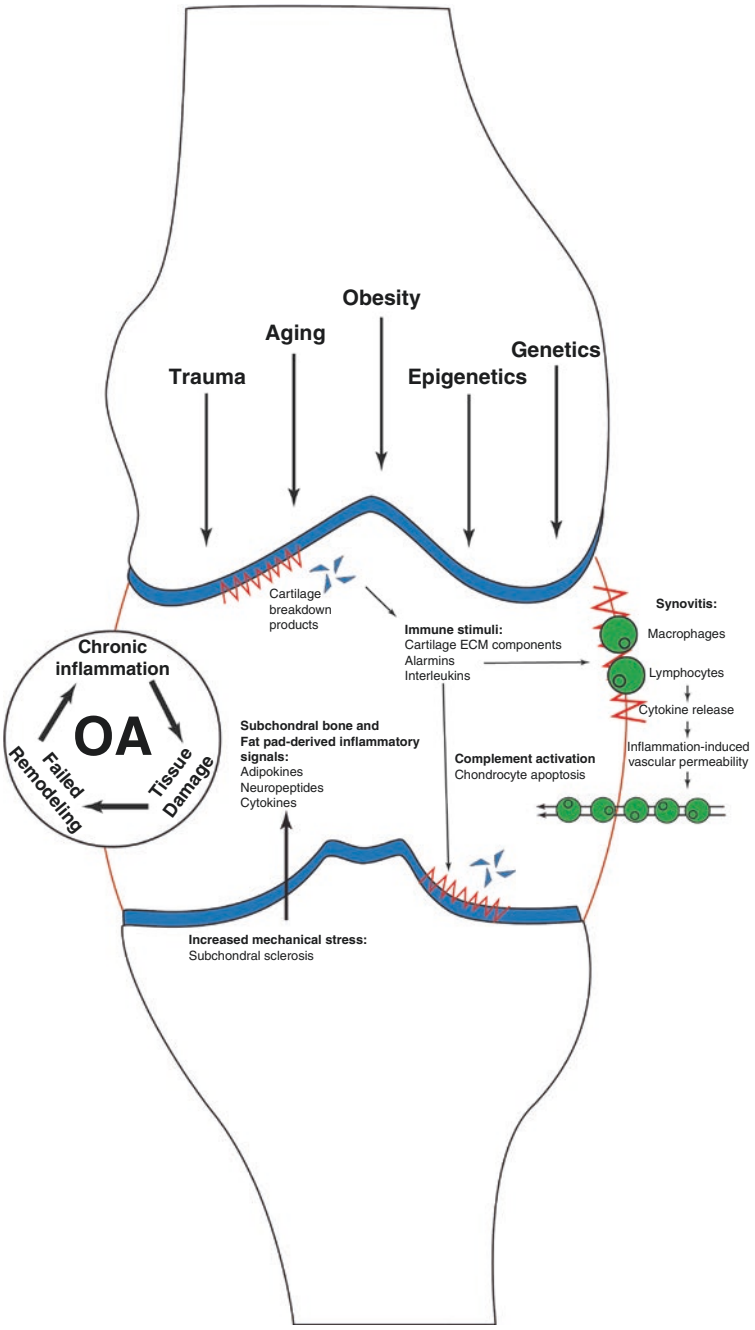

Fig. 3.1 OA pathophysiology. The pathophysiology of OA involves a variety of systemic and local factors, including trauma, aging, obesity, epigenetic, and genetic factors. Chronic inflammation plays a strong role, including inflammatory signals from local (cartilage breakdown products stimulating the innate immune system) and distant (adipose tissue-derived adipokines) sources. The end result is chronic tissue damage which does not undergo appropriate wound healing

Table 3.1 Pathophysiology

Mechanism	Consequence
Aging	Increased cellular senescence Increased systemic inflammation Reduced ability of periarticular structures to absorb stress
Genetic risk	Unclear. Potential defects in growth and remodeling, potential defects in vitamin A metabolism, cartilage calcification
Epigenetic risk	Create a gene regulatory environment permissible for overexpression of cartilage-destroying enzymes, inflammatory cytokines. Downregulation of collagen. May mediate, in part, aging risk
Trauma	Produces localized cartilage defects, increased extracellular matrix breakdown products, increased stress on subchondral bone, musculature, ligaments
Inflammation	Chronic systemic inflammation stimulated by cartilage breakdown products. Synovitis further stimulates immune responses, increases vascular permeability, and allows additional inflammatory cells to migrate to joint tissues. ECM breakdown also assembles complement and increases destruction of cartilage cells
Obesity	Increases systemic inflammation, leading to paracrine effects, further worsening chronic joint inflammation. Increases joint load

Among the first changes in OA joints are inflammation within the synovial lining (synovitis), focal changes within bone marrow underlying the joint (bone marrow lesions, characterized by fibrosis, necrosis, and trabecular abnormalities), and matrix changes within the cartilage itself [7, 8]. The end-stage pathology of OA consists of erosion of articular cartilage, subchondral bone change, and loss of function of the joint "unit" in diarthrodial joints. Grossly, OA joints exhibit joint space narrowing, subchondral sclerosis of underlying bone, hypertrophic osteophyte formation of neighboring bone, and subchondral cyst formation. Moderate-to-severe cases of OA may demonstrate fibrillated cartilage, especially in areas of maximal loading, an irregular and disordered attempt at cartilage regrowth [9]. We will briefly discuss each of these joint components individually.

Articular cartilage undergoes substantial changes during the development of OA. Although the majority of the physical load of a joint is borne by extra-articular structures (musculature, menisci, subchondral bone), normal cartilage provides a remarkably low-friction surface for smooth movement of a joint throughout its range of motion. Cartilage itself is made up of relatively scant, long-lived, metabolically inactive chondrocytes embedded within a tightly woven extracellular matrix (ECM) consisting of collagen fibers and proteoglycans coated by lubricin, a protein which reduces friction [10]. As OA develops, chondrocytes begin to proliferate and aggregate into nests, and switch from an anabolic gene transcription program to a catabolic one. Counterintuitively, this switch results in the production of matrix metalloproteinases and other enzymes which begin actively breaking down neighboring ECM, led principally by the actions of ADAMTS5 and the matrix metalloproteinases MMP-9 and MMP-13 [11]. Large shifts in epigenetic regulation occur within OA chondrocytes, providing a gene transcription regulatory pattern permissive for these changes [6, 12]. Remarkably, this transcriptomic shift closely

resembles cellular changes seen in the senescence-associated secretory phenotype (SASP) of senescent cells seen in other body tissues, leading some to speculate that the predilection for OA development later in life is due, at least in part, to age-related senescence [13].

Although the inciting event(s) remain unclear and are most likely multifactorial, a proinflammatory environment is created once cartilage breakdown begins which propagates and further accelerates OA joint damage. A variety of ECM components stimulate the innate immune receptors of macrophages and other antigen-presenting cells via toll-like receptors (TLRs) recognizing danger-associated molecular patterns (DAMPs) [14, 15]. This immune stimulation, and the cytokine production that results from it, further stimulates the production of catabolic enzymes. The complement cascade is important as well, as cartilage ECM components also catalyze the assembly of various complement proteins, further disrupting cartilage homeostasis. Elevations of inflammatory markers, including tumor necrosis factor-alpha (TNF alpha) and interleukin-6 are seen in synovial fluid of patients with progressive OA [16]. Furthermore, low-level systemic inflammation is also seen in patients with OA. For example, baseline prostaglandin E2 synthase levels in peripheral blood leukocytes can easily distinguish OA patients from controls, and a variety of cytokines, including interleukin-1 beta, TNF alpha, and cyclooxygenase 2 are increased in OA peripheral blood leukocytes and predict future rapid radiographic progression [17].

Cartilage is not the only tissue which undergoes extensive alteration during the development of OA. The *subchondral bone* plate is a thin cortical lamella directly underlying calcified cartilage. Although it is not a trabecular structure, it nonetheless has quite high porosity and contains channels for arteries, veins, and nerves, which can reach up to the cartilage surface [18]. During OA development, stress on the subchondral bone plate underlying damaged cartilage regions increases substantially, resulting in reactive thickening [19] and leading to the radiographic appearance of subchondral sclerosis. Inflammatory markers released during this bone remodeling process can reach the overlying articular cartilage [20]. Osteophytes, another hallmark feature of OA, originate in the periosteum [21] next to the bone/cartilage interface. They are a reactionary feature thought to develop in response to joint instability; one key player in the development of osteophytes is bone morphogenic protein-2 (BMP2) [22]. Interestingly enough, the inflammatory cytokine (and target of rheumatoid arthritis drugs) TNF alpha also plays a role in osteophyte formation [23]. Bone marrow lesions are present in symptomatic OA joints as well. Sometimes erroneously referred to simply as bone marrow "edema," these are defined as discrete regions of hyperintense marrow signal in fat-suppressed magnetic resonance imaging sequences. Gene transcription analysis of these lesions demonstrates substantial upregulation of genes involved in pain sensitization, extracellular matrix, and proinflammatory gene signaling [24]. The baseline volume of these lesions in OA patients is highly correlated with both joint pain and future radiographic narrowing of OA-affected joints [25].

Unlike cartilage, *synovium* is richly innervated and highly vascularized. Early OA is characterized almost universally by a degree of synovial inflammation, or synovitis. This is characterized by distinct histological findings, including syno-

vial hypertrophy and hyperplasia, infiltration by mononuclear cells (T and B lymphocytes, tissue macrophages, monocytes), and increased angiogenesis. Inflamed synovial tissue itself releases a variety of proinflammatory cytokines and catabolic factors in OA, including interleukins, TNF alpha, matrix metalloproteinases, bone morphogenic proteins, and pain-producing neurotransmitters (i.e., nerve growth factor, substance P) [26, 27]. Although it may not be as clinically apparent as the florid synovitis seen in autoimmune forms of arthritis, MRI-detectable synovitis is strongly correlated with knee radiographic OA severity [28]. This is not limited only to large-joint OA; the interphalangeal joints of hand OA patients also demonstrate increases in synovitis compared to non-OA controls, which correlates with both pain and radiographic severity [29]. As one might expect, patients with the erosive hand OA subtype exhibit additional increases in joint synovitis scores [30].

Risk Factors for OA Development

Genetics certainly play a role in the development of OA. The overall genetic contribution to OA can be estimated through the use of twin studies, where a comparison is made between the "shared" genetic risk of identical, monozygotic twins and compared to the "half-shared" genetic risk of fraternal, dizygotic twins. Older twin studies of hip OA studies, including the UK Adult Twin Registry, have estimated genetic contributions to hand OA at around 50% and hip OA at around 60% [31]. A newer study published in 2018 used more advanced data modeling techniques to adjust for modifiable risk factors and included a large number (n = 18,058) of twins from Norway [32]. Their model suggested that 73% of hip and 45% of knee variance was genetically determined.

Investigations into individual genetic risk alleles (*single nucleotide polymorphisms*, SNPs) in OA have been somewhat less fruitful, and are quite specific to joint site (hand vs. hip vs. knee). The largest genome-wide association studies (GWAS) have been performed in knee and hip OA. The only risk alleles that have been independently confirmed for knee OA include mutations in the collagen gene *COL11A1* and vascular endothelial growth factor *VEGF* [33]. Another gene, growth differentiation factor 5 (*GDF5*), deserves special mention. This gene and the rs143383 SNP located within it have been strongly associated with both hip and knee OA in both humans and mice; furthermore, the risk allele causes reduced gene expression in joint tissues [34–37]. *GDF5* is also under epigenetic control via changes in DNA methylation, and this conspires with underlying genetic changes to modulate gene expression further [38]. Relatively fewer genetic studies have been performed in hand OA; in fact, only two large GWAS studies have been completed to date. The first study, in 2014, found an association with the retinaldehyde dehydrogenase gene *ALDH1A2*, involved in vitamin A metabolism [39]. The second study, published in 2018, identified changes within the matrix GLA protein (*MGP*) gene, involved in cartilage calcification [40].

Epigenetics also play a role in OA development, as mentioned previously. A number of epigenome-wide association studies have been performed in both hip

and knee OA, and have both identified and confirmed a number of genes and genetic pathways as strongly dysregulated in OA cartilage and subchondral bone [6, 12, 41–44], including a number of inflammatory pathways and inflammation-related transcription factors. As in genetics, epigenetic patterns are distinctly geographic (different in knee OA samples compared to hips).

The strongest *environmental risk factor* for OA is advanced age, although how exactly age contributes to OA is still somewhat unclear. Aging increases levels of c-reactive protein (C-RP), interleukin 6 (IL6), and tumor necrosis factor alpha (TNFα), a phenomenon known as "inflammaging" [34]. Levels of systemic inflammatory mediators correlate with knee pain and decreased functional capacity in older adults with knee OA [35, 36]; furthermore, elevated levels of C-RP and IL6 are found in patients with knee OA and the level of these markers are related to the risk of OA progression [37, 38]. A dysregulated epigenome appears at least partly responsible for this phenomenon [39]. For example, using a DNA methylation-based age estimator, OA cartilage has been shown to be epigenetically "older" than control cartilage [45]. Autophagy, the process by which normal cells "clean up" old proteins, is defective in both aging and in OA articular cartilage and has been proposed as another possible explanation for the increased risk of OA associated with aging [46]. Supporting this theory, aged mice also demonstrate a reduced autophagy phenotype in cartilage, and this defect precedes the development of OA-like cartilage damage [47].

Another quite important risk factor for OA development is *obesity*. Notably, like epigenetic and genetic risk, the risk conferred by obesity varies by joint. In knees, those with the highest body mass index (BMI) have an approximate 8.5-fold increased risk for OA compared to individuals with a "normal" BMI [48]. Even more striking, each 2-unit increase in BMI equates to an increase in OA risk by 1.36-fold. A recent meta-analysis of 14 studies confirmed this finding that being overweight increased the risk of knee OA by 2.45-fold and obesity carried an increased risk of 4.55-fold [49]. In hips, the risk is somewhat lower, with increased risk of around 1.1-fold [50]. Hand OA is also associated with obesity, with increased risk in the 1.1-fold range [51]. How obesity contributes to OA pathogenesis is complex and is not simply related to increased stress on the joint itself; rather, it likely also involves the increased basal systemic inflammation related to obesity, as well as an increased production of "adipokines," inflammatory signaling molecules originating in adipose tissue [52, 53].

Trauma and "traumatic" occupations also increase the risk of OA. Dock workers, agricultural workers, carpenters, and cleaners have an increased risk of OA [54, 55]. Perhaps counterintuitively, running does not carry an increased risk for OA [56], nor does running worsen OA when it already is present [57]. However, "elite" athletes, mainly those with a history of high impact activities, do have a higher chance of developing OA as they age [58]. A history of previous injury is strongly associated with OA; this is perhaps best seen in the military population, where soldiers are more than five times more likely to develop PTOA compared to the general population. Soldiers with a history of knee joint trauma during active duty have a 5.7-fold increased risk of knee OA compared to those without a history of trauma [59].

Clinical Presentation

The clinical presentation of OA can vary dramatically between individuals, although the unifying feature in nearly all patients is *pain* (Table 3.2). The pain associated with osteoarthritis is distinct from autoimmune-related arthritis in that it is associated with minimal (generally <30 minutes) of morning stiffness and is characterized by worsening with activity. Researchers have been quite interested over the past several years in identifying the earliest pain patterns seen in OA to improve early diagnosis. The most detailed analysis of these patterns was published in 2014, based on the large, longitudinal Osteoarthritis Initiative (OAI) study [60]. They analyzed nearly 5000 individuals who developed knee OA during the study, retroactively examining their data for the first signs and symptoms, and identified pain on using stairs was the first positive symptom, followed by pain on walking, later pain on standing without walking, pain on lying or sitting, and finally, pain in bed. Others have previously identified similar "stages" of pain in OA, including Stage 1, being defined as predictable sharp pain on high-impact activity, Stage 2, constant pain

Table 3.2 Clinical presentation

OA-involved joint	Clinical presentation	Radiographic appearance
Knee	*Early*: pain on strenuous activity, walking up or down stairs *Intermediate*: pain in everyday activity *Late*: constant rest pain	*Early*: tibial spine sharpening, subchondral sclerosis, subchondral cyst formation *Intermediate*: joint space loss (usually medial>lateral), marginal osteophyte formation *Late*: complete cartilage loss, bone-on-bone appearance, joint deformity
Hip	*Early*: occasional pain on activity, referred to groin or to knee; pain on internal rotation or full flexion *Intermediate*: pain with activity, walking *Late*: constant rest pain	*Early*: asymmetrical joint space narrowing *Intermediate*: diffuse joint space loss, subchondral sclerosis *Late*: marginal osteophyte formation, bone-on-bone appearance
Hand	*Early*: occasional stiffness and pain on repetitive motion *Intermediate*: predictable pain with certain movements, stiffness daily, Heberden's and Bouchard's nodes may develop *Late*: pain with minimal movement, perceived loss of hand "strength"	*Early*: DIP and thumb 1st CMC joint space narrowing *Intermediate*: Substantial joint space narrowing, marginal osteophyte formation *Late*: Fixed flexion deformities develop, marginal osteophyte formation may cause lateral or medial distal phalanx deviation
Hand: erosive OA subtype	Rapidly progressive PIP, DIP joint pain and stiffness with significant synovitis	Characteristic "gull-wing" and "sawtooth" appearance of DIP, PIP, respectively. Substantial soft tissue swelling. Spontaneous joint fusion may occur. Significant marginal osteophyte formation and bony proliferation

that starts to affect daily activities, and Stage 3, consistent, dull or aching pain that is punctuated by periods of intense pain which severely limits range of motion and joint function [61]. The specific location of knee OA-related pain is related to the compartment affected, with localized anteromedial pain (medial compartment) or anterior pain (patellofemoral compartment) being common [62]. Hip OA generally presents as groin pain, although it can radiate down the leg and be misinterpreted as knee pain. Both active and passive movements, especially internal rotation of the hip while flexed, is a characteristic finding [63].

Other frequently-occurring signs and symptoms include bony hypertrophy, reflecting osteophyte formation (see section "Pathophysiology"), which tends to occur on marginal surfaces of OA-affected joints. Osteophyte formation and/or cartilage degradation can lead to frank joint deformities, which subsequently lead to joint instability. In fact, joint "buckling" or "giving out" is a very common symptom, particularly of knee OA. Over a quarter of patients with physician-diagnosed knee osteoarthritis will report knee instability symptoms, and a substantial number of these also report falls. Frequent falls in elderly OA patients can lead not only to fractures and other sequelae, but perhaps even more damaging, to fear of falling and poor balance confidence which can reduce physical activity further and worsen pre-existing deconditioning [64].

Hand OA generally affects the distal interphalangeal joints (DIP), first carpometacarpal joint (CMC, base of the thumb), proximal interphalangeal (PIP) joints, and occasionally the index and long finger metacarpophalangeal (MCP) joint, especially in cases associated with calcium pyrophosphate deposition disease. Like large-joint OA, hand OA is generally characterized by pain with activity. Some patients may complain mainly of stiffness, although this is generally less prolonged than autoimmune causes of hand arthritis. A frequent finding in hand OA are Heberden's (DIP) and Bouchard's (PIP) nodes. The appearance of these nodules is the result of early inflammation at the insertion of ligaments on the phalanges [65], further reinforcing the role of inflammation in OA. A less common but more aggressive variant of hand OA, known as *erosive OA*, is characterized by synovitis of the DIP joints with more extensive pain, erythema, and tenderness than one would expect of typical hand OA [66]. Erosive OA tends to progress more rapidly than traditional hand OA. Cartilage and joint capsule erosion lead to lateral DIP instability and sclerosis, causing characteristic "twisting" and lateral deviation of the distal phalanges, with eventual and spontaneous DIP fusion a common finding. As one might expect, this erosive form of OA carries with it worse functional outcomes [67].

Diagnosis

We lack well-defined criteria for the diagnosis of OA; most practitioners use a combination of symptoms and x-ray findings, although such definitions can be overly restrictive and lead to prevent early diagnosis. There are no formalized diagnostic criteria put forth by any of the major research societies, although classification

criteria do exist from the American College of Rheumatology, for hip, knee, and hand OA (Table 3.3). They suggest a diagnosis of knee OA with greater than 3 of the following: age greater than 50, less than 30 minutes of morning stiffness, with crepitus, bony tenderness, bony enlargement, and no palpable synovitis [68]. Hip guidelines are similar, with the addition of range of motion restriction and an allowed increase in morning stiffness threshold to 60 minutes [63]. The ACR hand OA criteria rely on bony enlargement of hand joints in addition to pain, aching, or stiffness [69]. It should be stated that these classification criteria have a variety of faults, perhaps most notably their lack of ability to capture early OA patients, where pain on activity is the predominant symptom and in which the development of osteophytes has not yet occurred.

When the suspicion for OA is high based on clinical symptoms, there is not generally an indication for additional testing, and empiric treatment can commence. The presence of atypical symptoms may, however, indicate the need for additional workup; these include rapid progression of pain (imaging may be necessary here), a clear-cut periodicity of symptoms (periodic symptoms self-resolving after just a few days to weeks is suggestive of a crystal arthritis), or other constitutional symptoms such as weight loss, fevers, recent or current infections, etc. Testing for autoantibodies associated with rheumatoid arthritis (rheumatoid

Table 3.3 ACR classification criteria [63, 68, 69]

Joint involved	Classification criteria (using history and physical examination)
Knee	Pain in the knee and at least 3 of: >50 years of age Less than 30 minutes of am stiffness Crepitus on active range of motion Bony tenderness Bony enlargement No palpable warmth of synovium
Hip	Pain in the hip and: >50 years of age Internal hip rotation ≥15 degrees Pain associated with internal hip Morning stiffness of the hip less than 60 minutes Or Internal hip rotation <15 degrees Hip flexion ≤115 degrees
Hand	Pain, aching, or stiffness in the hand and at least 3 of: Bony enlargement of 2 or more of: 2nd and 3rd distal interphalangeal (DIP) 2nd and 3rd proximal interphalangeal (PIP) 1st carpometacarpal joint of the thumb (CMC) Bony enlargement of 2 or more distal interphalangeal (DIP) Less than 3 swollen MCP joints Deformity of at least one of: 2nd and 3rd distal interphalangeal (DIP) 2nd and 3rd proximal interphalangeal (PIP) 1st carpometacarpal joint of the thumb (CMC)

factor and anti-cyclic citrullinated peptide), along with systemic inflammatory markers (erythrocyte sedimentation rate or c-reactive peptide) can be useful in ruling out an autoimmune cause of arthritis symptoms in patients with a more inflammatory presentation.

Radiography is not generally indicated for the diagnosis of OA but can be useful in ruling out alternative causes for arthritis, making a diagnosis of erosive OA, and in monitoring the degree of cartilage loss if one is considering joint replacement. Moderately to severely affected OA joints are characterized radiographically by joint space narrowing (generally asymmetrical), subchondral sclerosis, marginal osteophyte formation, and the presence of subchondral cysts. Hand and knee radiographs are frequently obtained in patients with OA-like symptoms to rule out cartilage calcification, which is suggestive of concomitant calcium pyrophosphate deposition disease. Erosive OA of the hands is associated with a particular appearance of DIP joints, including cartilage erosion leading to a "gullwing" pattern in DIP joints and/or "sawtooth"-type pattern in PIP joints [70]. Magnetic resonance imaging (MRI) can allow for direct quantitation both of synovitis, cartilage thickness, and screen for the presence of chondral lesions. Although MRI screening and monitoring of OA is not routinely done, it can predict patients who will have subsequent clinical OA progression [71]. Finally, synovial fluid analysis is not generally indicated to diagnose OA; however, it can be quite useful in ruling out alternative diagnoses, particularly the crystalline arthropathies.

Treatment

Although there are several in development, there are as yet no disease-modifying anti-osteoarthritic drugs (DMOADs) available for the treatment of OA. Therapeutic efforts, therefore, focus on improvements in physical function and pain relief. A well-conceived OA treatment plan should include efforts in three domains: attention to modifiable risk factors, including weight loss if at all possible, physical therapy regimens including an exercise and strengthening program, and pharmacologic and/or surgical treatment tailored to the individual needs and additional medical comorbidities of the patient (Table 3.4). We will consider each of these individually.

First, *modifiable risk factors* should always be addressed. Weight loss should be discussed with every OA patient, and dietary changes made (including referral to a dietician if necessary) to achieve sustained weight loss. Several studies have indicated that even as little as 10% weight loss has substantial benefits in reducing OA-related pain and decreasing functional disability in OA patients. For example, a recent large study combined dietary and exercise interventions in knee OA patients and resulted in a mean weight loss of 11%. In the intervention group, significant reductions in pain and improvements in function were noted, along with better physical health-related quality of life scores and even reductions in serum levels of

Table 3.4 Treatment

Treatment intervention or drug	OA subtype where specific treatment is appropriate (knee-only vs. multi-joint, with vs. without comorbidities)
Land-based exercise	*All*
Water-based exercise	*All*
Weight management	*All*
Strength training	*All*
Intra-articular steroid injection	*All*
Oral nonselective NSAIDs	Knee-only and multijoint OA without comorbidities
Oral COX2-selective NSAIDs	Knee-only and multijoint OA without comorbidities, or with up to moderate comorbidity risk
Topical NSAIDs	Knee-only OA both with and without comorbidities
Duloxetine	*All*
Acetaminophen	Appropriate for knee-only and multijoint OA without comorbidities. (∗Note: more recent data suggest benefit no greater than placebo)
Hyaluronic acid	Uncertain for knee-only OA, not appropriate for multijoint OA
Opioids	Uncertain for all forms of OA
Glucosamine/ chondroitin	Not recommended for any form of OA

Adapted from 2014 OARSI guidelines for treatment of knee OA [77]

the inflammatory cytokine interleukin 6 (IL6) [72]. Bariatric surgery, both for the treatment of OA and as an adjunct to total joint replacement, has been the focus of recent interest. Although studies have shown that massive weight loss induced by bariatric surgery does improve both pain and serum inflammatory markers in knee OA [73], several studies have also shown that bariatric surgery before joint replacement does not improve postarthroplasty functional or pain outcomes [74]. There have not been definitive studies to indicate that one particular diet is any better than another for the treatment of OA symptoms, and no dietary supplements have been shown effective for OA.

Physical therapy should be a part of every OA prescription. *Exercise* in essentially any form is beneficial in OA and should be part of every OA treatment plan. There do not appear to be differences between land-based and water-based exercise from an efficacy standpoint, and the beneficial effects of exercise last for up to 6 months after cessation (although patients should be encouraged to continue an exercise regimen indefinitely) [75]. Tai Chi, a Chinese martial art practiced with slow, methodical movements and an emphasis on balance, has a similar benefit in improving OA pain, physical function, and quality of life when compared to physical therapy regimens, with the added benefit of improving depression in OA patients [76].

Pharmacologic treatment in OA consists of a stepwise approach to analgesia. The best practice guidelines for the treatment of knee and hip OA come from several national and international societies, including the Osteoarthritis Research

Society International (OARSI), the American College of Rheumatology (ACR), and the American Academy of Orthopedic Research (AAOS). The most recently updated of these are the OARSI guidelines for the management of knee osteoarthritis [77], and will be the basis for the following recommendations. Contrary to popular practice, acetaminophen has little place in the modern treatment of OA, as it has been demonstrated in multiple meta-analyses to be no better than placebo at pain relief in OA [78]. The first question when treating a patient with OA regards their comorbidities. These include comorbidities which place the patient at moderate risk, including diabetes, advanced age, hypertension, cardiovascular disease (CVD), acute renal failure, history of gastrointestinal (GI) complications, depression, or physical impairment resulting in severe limitation of activity or exercise, including obesity. High-risk comorbidities include a history of a GI bleed, history of myocardial infarction, and chronic renal failure. Patients are then subdivided into knee-only OA or multijoint OA.

For knee-only OA without comorbidities, pharmacologic treatment may include nonsteroidal anti-inflammatory medications (NSAIDs), either "traditional" nonselective NSAIDs (i.e., naproxen), or COX-2-selective NSAIDs (i.e., celecoxib), or via topical application (i.e., diclofenac gel), or intra-articular (IA) therapies. Knee-only OA with comorbidities should avoid systemic nonselective NSAIDs and use instead IA treatments and topical NSAIDs. Multijoint OA benefits from systemic NSAIDs and IA treatments; generally, topical NSAIDs are not recommended, as the maximum dose may be inadequate to treat all involved joints. Multijoint OA in patients with comorbidities represents a challenge, with IA therapy and COX-2-selective NSAIDs being the preferred pharmacologic agents.

There have been surprisingly few head-to-head studies comparing the efficacy of various individual NSAIDs. One recent large meta-analysis including 76 individual trials suggested that the most effective oral NSAID for pain relief in OA was diclofenac at a dose of 150 mg total daily dose, followed by ibuprofen at 2400 mg total daily dose and naproxen at 1000 mg total daily dose [79]. This should be interpreted with caution, however, given the lack of direct comparison in published data. There was some concern recently over the cardiovascular safety of COX-2-selective NSAIDs (the one in the US market being celecoxib) when compared to nonselective NSAIDs; however, the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial, published in 2016, did not find evidence for an increased risk of celecoxib compared to either ibuprofen or naproxen [80]. One area where there is a clear difference based on COX selectivity is in the risk of GI bleed, where COX-2-selective NSAIDs are strongly superior to nonselective NSAIDs; in patients with a past history of GI bleed, topical NSAIDs should be used if at all possible, with COX-2-selective oral NSAIDs used cautiously, and consideration given to concomitant proton pump inhibitor therapy. Nonselective NSAID use should be avoided in these patients. Duloxetine, an oral serotonin-norepinephrine reuptake inhibitor (SNRI), is a nonopiate, non-NSAID alternative appropriate for OA treatment and has good evidence for its efficacy; it may be an appropriate choice in patients

with contraindications for NSAID or IA therapy or to be used in combination with NSAIDs [81]. Other oral pharmacologic therapies with dubious evidence for efficacy (and not recommended) include glucosamine/chondroitin, diacerein, both oral and transdermal opiates, and risedronate.

IA corticosteroid injections should also be considered. IA steroids have strong evidence for pain improvement in the short term, although longer-term data are lacking. A trial published in 2017 also demonstrated a statistically significant increase in the rate of cartilage loss after 2 years of every-three-month short-acting steroid injection, although the incremental cartilage loss was not likely to be clinically significant [82]. An extended-release steroid preparation of triamcinolone for IA injection has been recently approved which may offer both extended symptom improvement and a reduction in systemic side effects owing to a reduction in acute diffusion of steroid out of the joint [83]. The other intra-articular therapy frequently used for knee OA, hyaluronic acid, does not have robust support in the literature and has received either an "inappropriate" or "not certain" recommendation from OARSI [77, 84].

Surgical treatment is the only definitive therapy available to physicians for knee and hip OA at the present time and demonstrates substantial pain relief and improvement of physical function that are better than the best pharmacologic management. The benefits of joint replacement for OA should not be overstated, however, as a measurable percentage (up to one-third in some studies) of patients have persistent symptoms following arthroplasty [85]. The morbidity and mortality associated with joint replacement is low but should always be carefully considered before a decision is made to go to the operating room, with patient age and the presence of medical comorbidities (diabetes, obesity, and cardiovascular risks) being the strongest predictors of poor outcomes [86].

Questions

Scenario 1

A 65 year-old Caucasian woman (BMI 35, sedentary, history of GERD with a treated gastric ulcer 2 months ago) presents to your clinic complaining of a 1-year history of steadily worsening bilateral medial knee pain and hip pain, worse with exercise, better with rest. When asked, she has morning stiffness lasting less than 30 minutes in both of her knees. She does not complain of any periodicity (i.e., no "flares" lasting for days to weeks) in any of her joints. She has tried over-the-counter acetaminophen, up to 1000 mg three times daily, without any benefit.

Physical examination reveals an obese woman not in obvious distress. Her bilateral hips have range of motion limited to internal rotation of 12 degrees and flexion of 90 degrees. She has bony enlargement of both knees and a mild cool effusion. She has bony enlargement of her bilateral 1st carpometacarpal joints and two bilateral distal interphalangeal joints without an effusion.

1. For her potential knee OA, what additional testing (if any) is indicated at this time?

   A. Standing anterior/posterior radiographs
   B. MRI
   C. Joint aspiration with gram stain, culture, cell count with differential, and crystal analysis
   D. No additional testing indicated at this time

   Correct answer: D
   Critique: This patient meets ACR criteria for hip, knee, and hand OA. Her history and physical examination are not suggestive of an autoimmune arthritis (no substantial morning stiffness, no synovitis on examination), nor is it suggestive of a crystal arthropathy (no substantial periodicity, no history of podagra-like symptoms). Imaging is *not* indicated to make a diagnosis of OA; in fact, an MRI would almost certainly show cartilage defects given her bony hypertrophy. Joint aspiration is indicated only in the setting of symptoms suggestive of a septic joint, or a crystal arthropathy.
2. She asks about the risk of passing her arthritis on to her children. Which of her arthritic complaints are most likely genetic or hereditary?

   A. Hip OA
   B. Knee OA
   C. Neither is genetic
   D. Both have equal hereditary components

   Correct answer: A
   Critique: Both historical and modern twin studies suggest that hip, knee, and hand OA have a genetic component; however, the most recent data support the notion that hip OA has a substantially larger genetic component than does knee OA.
3. She prefers a nonoperative approach to the treatment of her multijoint OA. She has heard that physical activity can make her joints worse by "wearing them down." What is your response to this?

   A. This is true, OA patients should avoid physical activity, as it will only make their joints worse.
   B. We do not have clear data on this topic.
   C. Physical exercise is a cornerstone of OA therapy and will reduce OA-related pain even without additional interventions.
   D. Physical exercise may improve OA but should be utilized only after maximizing pharmacological therapy.

   Correct answer: C
   Critique: Multiple studies have indicated that physical therapy can have dramatic effects in improving OA patients' quality of life, pain, and physical function scores. The data are so strong, in fact, that they are the cornerstone of therapy for OA in the guidelines of all major OA-related societies, including the most recent OARSI recommendations. Physical exercise should be prescribed for all OA patients regardless of pharmacologic treatment.

4. Now having convinced her that she should pursue a physical exercise regimen, she wants to know which type of exercise will work the best for her. What is your response to this?

   A. Land-based exercise (running, walking).
   B. Water-based exercise (swimming, water aerobics).
   C. Yoga.
   D. A and B are equally effective.

   Correct answer: D
   Critique: Multiple studies have proven the benefits in both OA-related pain and disability for physical exercise, but no particular regimen is superior to the others. Therefore, OARSI recommends either a land-based or water-based regimen. Yoga has been studied but has not been shown to be superior to other exercise regimens. Tai Chi, a Chinese martial art with an emphasis on balance, has been extensively studied and may offer additional benefits beyond other forms of exercise, but does not yet carry a separate OARSI recommendation.
5. She would like to start a medication to help improve her multijoint OA, since acetaminophen has not helped her. She has considered taking over the counter nonsteroidal anti-inflammatory drugs (NSAIDs), like naproxen. What is your recommendation regarding this?

   A. Naproxen is recommended for multijoint OA; she should begin this treatment.
   B. Acetaminophen has been shown superior to oral NSAIDs and should be tried again in her case.
   C. There are no recommended oral medications for multijoint OA in her case.
   D. An oral nonselective NSAID is not the appropriate choice in this situation given her recent gastric ulceration; a medication like duloxetine may be more appropriate.

   Correct answer: D
   Critique: It is accurate that nonselective oral NSAIDs are recommended for multijoint OA, but she is a high-risk patient given her recent gastric ulceration. Preference would be to start with medications which do not carry a substantial GI risk; duloxetine is a recommended medication in the OARSI guidelines for a situation like this. If she fails duloxetine, consideration could be given to a combination of a COX2-selective NSAID (celecoxib) plus an oral proton pump inhibitor (omeprazole), although caution should be exercised.

Scenario 2

A 60 year-old African-American man (no significant past medical history, BMI 25) presents to your clinic complaining of steadily-worsening right knee pain over the past 2 years. He recalls injuring this joint when he was a teenager. He does not have periodic “flares” of pain, although he notes that his first pain in this joint started

when walking upstairs and it now bothers him walking on level ground. He has previously been told that he did not have joint space narrowing on plain radiographs done about 2 years ago. He has tried physical therapy, exercise, and topical and oral nonselective NSAIDs without any relief.

Physical examination reveals a mild cool effusion in the right knee with no active synovitis, and mild bony hypertrophy is present. He has no other joint abnormalities. You diagnose him with unilateral primary knee osteoarthritis.

6. He first asks whether he should take high-dose acetaminophen or glucosamine sulfate for his knee OA. What is your response?

   A. Either of these medications can be used; studies have indicated they are as effective as NSAIDs for relieving pain in knee OA.
   B. Neither of these medications has strong evidence of efficacy, and they are less likely to work than the NSAIDs he has previously tried.
   C. Glucosamine, but not acetaminophen, has strong evidence for its effectiveness and should be tried.
   D. Acetaminophen, but not glucosamine, has strong evidence for its effectiveness and should be tried.

   Correct answer: B
   Critique: A multitude of studies indicate that the effect on OA-related pain of acetaminophen is small and generally equivalent with oral placebo; NSAIDs have a much higher effect. Glucosamine has been shown in several meta-analyses to be no better than placebo for OA-related pain.
7. He asks if his previous injury decades ago has something to do with his OA. What is your response?

   A. Preceding joint injury is a strong risk factor for subsequent OA development.
   B. Joint injury decades ago is unlikely to have long-lasting consequences.
   C. Preceding joint injury has not been studied in the context of OA.
   D. Too much exercise following his joint injury, and not the injury itself, is likely the cause of his OA.

   Correct answer: A
   Critique: Preceding joint injury is one of the strongest risk factors for OA; this is perhaps best seen in the military population, where so-called post-traumatic OA (PTOA) is a major concern. Soldiers with a previous history of joint trauma have a roughly sixfold higher risk of subsequent knee OA than soldiers without a history of trauma. There is no evidence that postinjury exercise exacerbates OA.
8. He is tired of trying oral and topical medications that do not work and asks about potential intra-articular (IA) injections; specifically, he has friends who have told him steroids work. What is your response?

   A. There is no evidence for the efficacy of steroids in knee OA.
   B. There is evidence for IA steroids, but IA hyaluronic acid derivatives work better.

C. IA NSAIDs should be tried next.
D. IA steroids are an appropriate choice in his situation, and he should receive this treatment immediately.

Correct answer: D
Critique: The OARSI guidelines recommend a physical therapy and exercise regimen for all patients with knee OA and suggest first-line treatment with oral or topical NSAID agents. IA corticosteroids have strong evidence for efficacy, particularly in knee OA, and can be used as second-line agents. IA hyaluronic acid derivatives have less robust support in the literature, and only receive a conditional recommendation by OARSI. IA NSAIDs (ketorolac specifically) has been examined in a few small (positive) studies, but no large analyses have yet been done.

9. He asks if there are any supplements or dietary changes he should make at this time which would help his knee OA. What is your response?

A. No dietary changes or supplements have been definitively shown to improve OA pain or function.
B. He should follow a gluten-free diet.
C. He should take supplemental vitamin C.
D. He should follow a low-fat diet.

Correct answer: A
Critique: Although much has been made in the lay media regarding the effects of particular diets on joint pain, no large, well-conducted studies have ever demonstrated a benefit of a particular diet in OA patients.

10. He has heard "horror stories" about individuals having substantial pain following knee replacements, and wants to know if arthroplasty, on average, offers "better" pain relief for knee OA than injections or other medications. What is your response?

A. Joint arthroplasty is often the only treatment available for end-stage OA, although the data suggest that it is not as effective as oral medications at treating OA pain.
B. Joint arthroplasty is not only effective but has a very low (<5%) incidence of postoperative pain persistence.
C. Joint arthroplasty and oral NSAIDs are roughly equivalent at relieving pain.
D. Joint arthroplasty has the strongest pain-relieving effect of any intervention for knee OA at the present time, although it does carry a risk (up to one-third of patients) of persistent postop pain.

Correct answer: D
Critique: Although no panacea, joint arthroplasty generally offers an effect size on OA-related pain (difference in pain improvement with intervention subtract pain improvement with placebo) roughly double that of any intra-articular, oral, or topical OA drug. The decision to pursue joint arthroplasty should not be taken lightly, but nevertheless strongly considered once more conservative treatments have failed.

Scenario 3

A third-year medical student on a rheumatology rotation is researching OA and has a few questions.

11. "I have heard that OA is a wear-and-tear phenomenon, caused by repetitive joint damage wearing away cartilage, is that true?"

    A. Although microtrauma may play a role, OA is not a wear-and-tear phenomenon, and instead is a systemic, chronic, low-level inflammatory disease.
    B. OA is indeed a wear-and-tear disease limited to specific joints.
    C. OA is a fully genetic disease, we just have not isolated the causative gene yet.
    D. OA is a systemic autoimmune disease.

    Correct answer: A
    Critique: Multiple lines of evidence support the fact that OA is a systemic, chronic, low-level inflammatory disease. It is not a result of wear-and-tear; in fact, physical activity improves OA symptoms. Several well-controlled, large genetic association studies have been performed on OA and have revealed single nucleotide polymorphisms (SNPs) with relatively low contribution to the disease; it is certainly not a fully genetic disease. Finally, OA as we currently understand is not a systemic autoimmune disease and does not generally respond to autoimmune disease-targeted therapy.
12. "I have heard a lot about epigenetics lately in several chronic diseases, does OA pathogenesis have anything to do with this?"

    A. No, OA is a purely physical phenomenon.
    B. Yes, research has indicated substantial OA-related epigenetic changes within joint tissues, which point toward a potential role in pathogenesis.
    C. No, OA is a purely genetic disease.
    D. Not sure, no studies have been performed in this regard.

    Correct answer: B
    Critique: Neither a purely physical nor genetic disease, multiple lines of evidence have recently shown that substantial epigenetic changes exist within OA tissues, particularly within cartilage and subchondral bone, and are related to chronic inflammatory pathways. This may be a way in which environmental perturbations (trauma, aging, inflammation) interact with underlying genetic risk to lead to the development of OA.

Scenario 4

A 75 year-old Latina woman presents to your office complaining of a 6-month history of steadily worsening distal interphalangeal (DIP) pain in the index fingers of both hands. She has noticed some swelling, heat, and warmth, and they seem

to be worsening steadily. She has about 45 minutes of stiffness of these joints every morning, and then they hurt when she is using (flexing) them. She has no personal or family history of psoriasis, ankylosing spondylitis, or inflammatory bowel disease.

Physical exam shows an otherwise healthy woman with swelling, warmth, and mild heat of her index finger DIPs bilaterally. She has joint space loss, restriction in range of motion, and a mild lateral deviation of her distal phalanx bilaterally.

13. What radiographic findings would be most consistent with this patient's most-likely diagnosis?

    A. Subchondral cysts at the distal portion of the middle phalanx bilaterally
    B. Chondrocalcinosis of the affected DIP joints bilaterally
    C. Central cartilage erosions with gullwing formation
    D. Marginal erosions

    Correct answer: C
    Critique: This patient is presenting with likely erosive OA, an aggressive subtype of OA which presents generally with mild synovitis and is rapidly progressive. A characteristic radiographic finding is central cartilage erosions forming a "gullwing" or "sawtooth" sign. Subchondral cysts would be expected with traditional OA, whereas chondrocalcinosis would be more typical for CPPD (and is unlikely to affect the DIP joints). Marginal erosions would be classic for an autoimmune type of arthritis; given the joints involved, consideration for a seronegative spondyloarthropathy.

14. She is concerned about the risks of starting an oral COX2-selective NSAID, as she has heard that heart disease risk is worsened in patients taking COX2-selective NSAIDs compared to nonselective NSAIDs. What is your response?

    A. This is accurate, COX2-selective NSAIDs have an increased relative risk of heart disease; in fact, this is why previous COX2-selective NSAIDs were removed from the US market.
    B. Nonselective NSAIDs have a higher cardiac risk.
    C. NSAIDs carry no additional risk of heart disease.
    D. COX2-selective and nonselective NSAIDs appear to have the same cardiac risk profile.

    Correct answer: D
    Critique: Although previous data had suggested a potential increase in cardiac risk among patients taking the COX2-selective drug celecoxib (approved in the USA), the large PRECISION trial, recently completed, found no additional risk when comparing celecoxib to naproxen and ibuprofen. Certainly, nonselective NSAIDs do not place an individual at a higher risk than a COX2-selective agent. Several meta-analyses do indicate that taking any oral NSAID does produce a somewhat increased risk of heart disease.

15. She has seen commercials for etanercept for the treatment of "hand arthritis" and asks if this would be appropriate for her. What is your response?

    A. OA is a noninflammatory disease, so a TNF inhibitor such as etanercept has no place in its management.
    B. Etanercept might be useful for the treatment of hand OA, it should be tried.
    C. Although OA is an inflammatory disease, etanercept has been tried and failed for hand OA and should not be used.
    D. Etanercept should be used only after failing an oral NSAID.

    Correct answer: C
    Critique: Several studies have examined the potential benefits of using rheumatoid arthritis-approved biologics (and oral DMARDs) in the treatment of hand OA, including erosive OA. None of these drugs have been confirmed as effective in the treatment of hand OA and place the patient at significant increased risk of adverse effects (i.e., infection). At this time, it is not recommended that hand OA patients be administered biologic drugs given their lack of efficacy.

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