

## Chapter 2

# Clinical Aspects: A Rheumatologist's Perspective

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• Symptomatic osteoarthritis • Diagnosis • Synovial joints  
• Synovitis • Effusion

### Introduction

From a rheumatologist's perspective, cartilage imaging is most significant in the setting of osteoarthritis. Symptomatic osteoarthritis (OA) causes substantial physical and psychosocial disability [1]. In the early 1990s, over 7 million Americans were limited in their ability to participate in their main daily activities, such as going to school or work or maintaining their independence – simply because of their arthritis [2]. Interestingly, the risk for disability (defined as needing help walking or climbing stairs) attributable to knee OA is as great as that attributable to cardiovascular disease and greater than that due to any other medical condition in elderly persons [1]. Like arthritis prevalence, the prevalence of arthritis-related disability is also expected to rise by the year 2020, when an estimated 11.6 million people will be affected [2].

Compounding this picture are the enormous financial costs that our nation bears for treating arthritis, its complications, and the disability that results from uncontrolled disease. The total annual cost in the United States is almost \$65 billion – a figure equivalent to a moderate national recession [3]. This amount includes an estimated medical bill of \$15 billion each year for such expenses as 39 million physician visits and more than half a million hospitalizations (CDC, 1999, unpublished data). OA accounts for 90% of hip and knee replacements [4]. The balance is largely due to

indirect costs such as those from wage losses [3]. Thus, arthritis has become one of our most pressing public health problems – a problem that is expected to worsen in the next millennium with the increasing prevalence of this disease.

This chapter delineates the characteristic symptoms and signs associated with cartilage loss and OA and how they can be used to make the clinical diagnosis with discussion of the role of imaging. The predominant symptom in most patients presenting with OA is pain. Over recent years a number of imaging-based studies have narrowed the discord between knowledge about structural findings on imaging and symptoms. The remainder of the chapter focuses on what we know causes pain in OA and contributes to its severity, with a predominant focus on imaging findings.

### What Is OA?

OA can be viewed as the clinical and pathological outcome of a range of disorders that result in structural and functional failure of synovial joints [5]. This highly prevalent disease occurs when the dynamic equilibrium between the breakdown and repair of joint tissues is overwhelmed [6]. The resulting progressive joint failure may cause pain, physical disability, and psychological distress [1], although many persons with structural changes consistent with OA are asymptomatic [7]. The reasons why there is this disconnect between disease severity and the level of reported pain and disability are largely unknown, although recent imaging studies are beginning to shed light on this.

Typically OA presents as joint pain. During a 1-year period, 25% of people over 55 years have a persistent episode of knee pain, of whom about one in six consult their general practitioner about it [8]. Symptomatic knee OA (pain on most days and radiographic features consistent with OA) occurs in approximately 12% of those aged over 55 [8].

While OA is common in the knee, it is even more prevalent in the hands, especially the distal (DIP) and proximal (PIP) interphalangeal joints and the base of the thumb (CMC). When symptomatic, especially so for the base of thumb joint,

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hand OA is associated with functional impairment [9, 10]. OA of the thumb carpo-metacarpal joint is a common condition that can lead to substantial pain, instability, deformity, and loss of motion [11]. Over the age of 70 years, approximately 5% of women and 3% of men have symptomatic OA affecting this joint with impairment of hand function [9].

The prevalence of hip OA is about 9% in Caucasian populations [12]. In contrast, studies in Asian, black, and East Indian populations indicate a very low prevalence of hip OA [13]. The prevalence of symptomatic hip OA is approximately 4% [14].

## What Are the Characteristic Symptoms of OA?

The joint pain of OA is typically described as mechanical; that is, exacerbated by activity and relieved by rest. More advanced OA can cause rest and night pain leading to loss of sleep which further exacerbates pain. The cardinal symptoms that suggest a diagnosis of OA include:

- Pain (typically described as activity-related or mechanical, may occur with rest in advanced disease; often deep, aching and not well localized; usually of insidious onset)
- Reduced function
- Stiffness (of short duration, also termed “gelling,” i.e., short-lived stiffness after inactivity)
- Joint instability, buckling or giving way
- Patients may also complain of reduced movement, deformity, swelling, crepitus, and increased age (OA is unusual before age 40) in the absence of systemic features (such as fever)
- When pain persists pain-related psychological distress

## Tailoring the Physical Exam: What Signs Are Associated with OA?

Physical examination should include an assessment of body weight and body mass index, joint range of motion, the location of tenderness, muscle strength, and ligament stability. For lower limb joint involvement, this should include assessment of body mass and postural alignment in both standing and walking [15]. The features on physical examination that suggest a diagnosis of OA include:

- Tenderness, usually located over the joint line
- Crepitus with movement of the joint
- Bony enlargement of the joint, e.g., Heberden’s and Bouchard’s nodes, squaring of the first CMC, typically along the affected joint line in the knee

- Restricted joint range of motion
- Pain on passive range of motion
- Deformity, e.g., angulation of the DIP and PIP joints, varus (bowed legs) deformity of the knees
- Instability of the joint
- Altered gait
- Muscle atrophy or weakness
- Joint effusion

## The Diagnosis of OA

Bearing in mind that radiographs are notoriously insensitive to the earliest pathological features of OA, the absence of positive radiographic findings should not be interpreted as confirming the complete absence of symptomatic disease. Conversely, the presence of positive radiographic findings does not guarantee that an osteoarthritic joint is also the active source of the patient’s current knee or hip symptoms, where other sources of pain including periarticular sources, such as pes anserine bursitis at the knee and trochanteric bursitis at the hip, often contribute [7]. According to the ACR criteria for classification of hand OA (unlike the hip and knee where radiographs enhance the sensitivity and specificity), X-rays are less sensitive and specific than physical examination in the diagnosis of symptomatic hand OA [16]. The usefulness of X-rays relates more importantly to the exclusion of other diagnostic possibilities rather than confirmation of osteoarthritic disease [17].

In clinical practice, the diagnosis of OA should be made on the basis of the medical history and physical examination, and the role of radiography is to confirm this clinical suspicion and rule out other conditions.

When disease is advanced, it is visible on plain radiographs, which show narrowing of joint space, osteophytes, and sometimes changes in the subchondral bone. MRI can be used in infrequent circumstances to facilitate the diagnosis of other causes of joint pain that can be confused with OA (osteochondritis dissecans, avascular necrosis). Laboratory testing has little role in establishing the diagnosis of OA. Because OA is a noninflammatory arthritis, laboratory findings are expected to be normal.

## What Are the Diagnostic Criteria for Osteoarthritis?

When making the diagnosis of OA, consider using the criteria of the American College of Rheumatology for diagnostic purposes and classification of OA of the hip, knee, and hands

in patients with pain in these joints [16, 18]. These are the criteria that are used in research studies and should be used to inform the diagnosis of OA in individuals, but not limiting the information gathering to these criteria and considering the wealth of other information that patients with OA may provide, which can help to either confirm or refute an OA diagnosis.

In the process of taking a history, it is important to ask how the pain has affected the person's function at home, work, and in recreational activities. Also, ask about how the person is coping with pain and how well that is going. It is important to look for signs of psychological distress, e.g., signs of anxiety such as excessive pain avoidant posturing, sleep onset insomnia, or signs of depression such as early morning wakening, weight loss, irritability, or a marked increase in memory/concentration problems.

## Factors That Contribute to Pain

The source of pain is not particularly well understood and is best framed in a biopsychosocial framework (posits that biological, psychological, and social factors all play a significant role in pain in OA) [19, 20].

From a biological perspective, neuronal activity in the pain pathway is responsible for the generation and ultimate exacerbation of the feeling of joint pain. During inflammation, chemical mediators are released into the joint, which sensitize primary afferent nerves such that normally innocuous joint movements (such as increased physical activity, high heeled shoes, and weather changes) now elicit a painful response. This is the neurophysiological basis of allodynia, i.e., the sensation of pain in response to a normally nonpainful stimulus such as walking. Over time this increased neuronal activity from the periphery can cause plasticity changes in the central nervous system by a process termed "wind-up." In this instance, second order neurones in the spinal cord increase their firing rate such that the transmission of pain information to the somatosensory cortex is enhanced. This central sensitization phenomenon intensifies pain sensation and can even lead to pain responses from regions of the body remote from the inflamed joint, i.e., referred pain.

Pain has long been recognized as a complex sensory and emotional experience [21]. Each individual has a unique experience of pain influenced by their life experience and genotypic profile. An individual's stable psychological characteristics (trait) and the immediate psychological context in which pain is experienced (state) both influence perception of pain. A full understanding of pain requires consideration of psychological and social environmental processes mediating a patient's response to their disease [22]. The

biopsychosocial model is a very useful approach to understanding and assessing the experience of pain in persons with OA [23]. Constitutional factors that can predispose to symptoms include self-efficacy, pain catastrophizing, and the social context of arthritis (social support, pain communication) are all important considerations in understanding the pain experience.

## Local Tissue Pathology

The structural determinants of pain and mechanical dysfunction in OA are also not well understood but are believed to involve multiple interactive pathways. In broad terms, there are a number of tissues within the joint that contain nociceptive fibers, and these are the likely sources of pain in osteoarthritis. The subchondral bone, periosteum, periarticular ligaments, periarticular muscle spasm, synovium, and joint capsule are all richly innervated and are the likely source of nociception in OA. In population studies, there is a significant discordance between radiographically diagnosed OA and knee pain [7]. While radiographic evidence of joint damage predisposes to joint pain, it is clear that the severity of the joint damage on the radiograph bears little relation to the severity of the pain experienced.

However, utilizing other imaging modalities such as magnetic resonance imaging (MRI), significant structural associations, such as bone marrow lesions [24, 25], subarticular bone attrition [26], synovitis, and effusion [27, 28], have been related to knee pain. It remains unclear which of these local tissue factors predominate as until recently these analyses did not account for the fact that much of the structural change is collinear (a person who has more severe disease will have worse structural change in multiple tissues including the bone, synovium, etc.) and were not adjusting for other tissue changes. A recent analysis confirmed most beliefs that it is likely that changes in the subchondral bone and synovial activation/effusion predominate [29].

The different tissues within the joint and their respective contribution to symptoms are discussed below.

## Hyaline Articular Cartilage

Articular cartilage is both aneural and avascular. As such, cartilage is incapable of directly generating pain, inflammation, stiffness, or any of the symptoms that patients with OA typically describe [30]. Given its relative unimportance to OA's symptomatic presentation, it is ironic that articular cartilage has received so much attention while other common

symptom sources in the joint are ignored. Some studies have suggested a relation between cartilage morphometry and lesions and the symptoms of OA [31]. It is important to note that this disease of the whole joint concurrently affects other tissues that do contain nociceptors. The studies that have demonstrated a relation of cartilage damage to pain have traditionally investigated the role of cartilage in predisposing to symptoms in isolation from other tissues and as such are fundamentally flawed. A recent study suggested that areas of denuded cartilage are related to symptoms [32]. Again, the likely mechanism for symptom genesis is through secondary mechanisms such as: (1) exposing the underlying subchondral bone and the inherent symptom genesis from this structural alteration, (2) vascular congestion of subchondral bone leading to increased intraosseous pressure, and (3) synovitis secondary to articular cartilage damage with activation of synovial membrane nociceptors.

### Subchondral Bone

Periarticular bone changes associated with OA can be segregated into distinct patterns based on the anatomic location and pathogenic mechanisms. These alterations include progressive increase in subchondral plate thickness, alterations in the architecture of subchondral trabecular bone, formation of new bone at the joint margins (osteophytes), development of subchondral bone cysts, and advancement of the tidemark associated with vascular invasion of the calcified cartilage.

Of these lesions that which has the most supportive evidence for a role in symptom genesis is the bone marrow lesion (Fig. 2.1). Lesions in the bone marrow play an integral if not pivotal role in the symptoms that emanate from knee OA and its structural progression [24]. Bone marrow lesions were found in 272 of 351 (77.5%) persons with painful knees compared with 15 of 50 (30%) persons with no knee pain ( $P < 0.001$ ). Large lesions were present almost exclusively in persons with knee pain (35.9% vs. 2%;  $P < 0.001$ ). After adjustment for severity of radiographic disease, effusion, age, and sex, all lesions and in particular large lesions remained associated with the occurrence of knee pain. More recently, their relation to pain severity [25] and incident pain [33] was also demonstrated. There is conflicting data albeit from smaller studies with different methods suggesting no relation of bone marrow lesions to pain [34, 35]; however, the balance of data would support a strong relation of bone marrow lesions to pain.

Other bone-related causes of pain include periostitis associated with osteophyte formation [36], subchondral microfractures [37], bone attrition [26], and bone angina due to decreased blood flow and elevated intraosseous pressure [38].



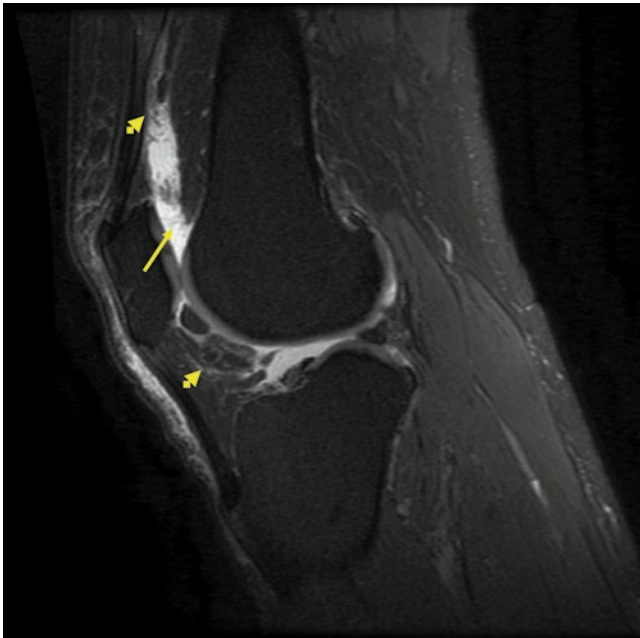
**Fig. 2.1** T2 weighted fat suppressed sagittal sequence depicting multiple diffuse hyperintensities (arrows) abutting the subchondral plate in the weight-bearing proximal tibia and trochlea characteristic of bone marrow lesions

The particular bone pathology most responsible for pain remains elusive; however, identifying this would be a major advance in delineating appropriate therapeutic targets. One likely source that remains underexplored is that of intraosseous hypertension. The pathophysiology remains unclear, although phlebographic studies in OA indicate impaired vascular clearance from bone and raised intraosseous pressure in the bone marrow near the painful joint [38–41]. What may subsequently cause pain is as yet unknown. Increased trabecular bone pressure, ischemia, and inflammation are all possible stimuli.

### Synovitis, Effusion

The synovial reaction in OA includes synovial hyperplasia, fibrosis, thickening of synovial capsule, activated synovocytes, and in some cases lymphocytic infiltrate (B- and T-cells as well as plasma cells) [42]. The site of infiltration of the synovium is of obvious relevance as one of the most densely innervated structures of the joint is the white adipose tissue of the fat pad, which also shows evidence of inflammation and can act as a rich source of inflammatory adipokines [43]. Synovial causes of pain include irritation of sensory nerve endings within the synovium from osteophytes and synovial inflammation that is due, at least in part, to the





**Fig. 2.2** Effusion (arrow) and peripatellar synovitis (arrowhead) on T2 weighted fat suppressed sagittal sequence. On noncontrast sequences such as this, the magnitude of synovitis is difficult to determine

release of prostaglandins, leukotrienes, proteinases, neuro-peptides, and cytokines [20, 44].

Synovitis and effusion are frequently present in osteoarthritis and correlate with pain and other clinical outcomes (Fig. 2.2) [27]. Synovial thickening around the infrapatellar fat pad using noncontrast MRI has been shown on biopsy to represent mild chronic synovitis [45]. A semiquantitative measure of synovitis from the infrapatellar fat pad is associated with pain severity, and similarly change in synovitis is associated with change in pain severity [28]. This study assessed 270 subjects (158 male, 112 female) with at least one follow-up MRI. Mean synovitis score at baseline was 3.3 (1.9) with an average change of 0.15 (1.5). There was a correlation of baseline synovitis with baseline pain score (Pearson correlation coefficient  $r=0.20$ ,  $p=0.0005$ ). Changes in summary synovitis score were associated with changes in pain over time ( $p=0.005$ ). An increase of one unit in summary synovitis score resulted in a 3.11 mm increase in VAS pain score (0–100 scale). Of the three locations for synovitis, changes in the infrapatellar fat pad were most strongly related to pain change (4.2 mm increase in pain per unit increase in synovitis).

In an important caveat to this analysis, a recent study compared nonenhanced proton-density-weighted fat-suppressed (PDFS) sequences with T1-weighted (T1w) fat-suppressed (FS) contrast-enhanced (CE) sequences for semiquantitative assessment of peripatellar synovitis in OA [46]. This data suggested that signal alterations in Hoffa's fat pad on nonenhanced images do not always represent synovitis as

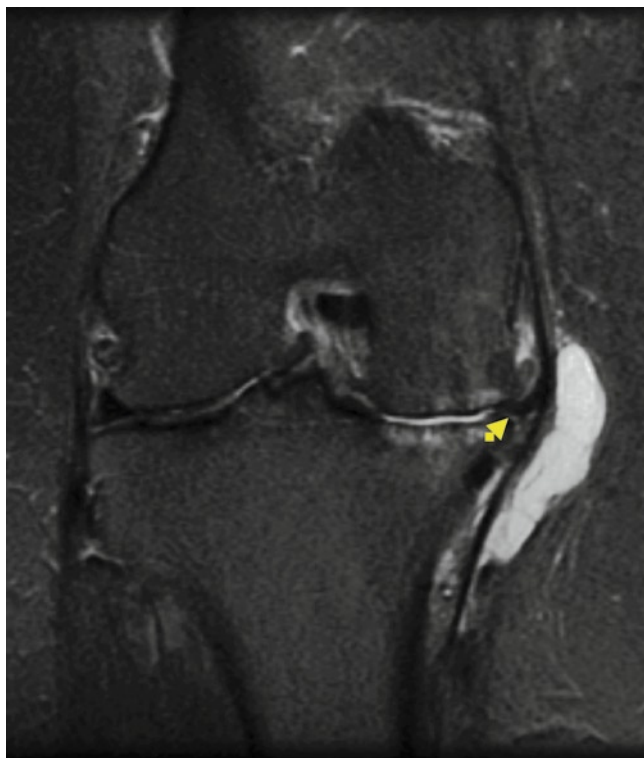
seen on T1w CE images but are a rather nonspecific albeit sensitive finding. Semiquantitative scoring of peripatellar synovitis in OA ideally should be performed using T1w CE sequences and should include scoring of synovial thickness.

## Meniscus

The meniscus has many functions in the knee, including loadbearing, shock absorption, stability enhancement, and lubrication [47, 48]. The menisci transmit anywhere from 45% to 60% of the compressive loads in the knee [47]. If the meniscus does not cover the articular surface that it is designed to protect due to change in position, or if a tear leaves it unable to resist axial loading, it will not perform this role. The absence of a functioning meniscus increases peak and average contact stresses in the medial compartment of the knee in a range of 40–700% [49–51].

Knee OA after meniscectomy/meniscal repair is traditionally considered a result of the joint injury that leads to the meniscectomy in the first instance and the increased cartilage contact stress due to the loss of meniscal tissue [52–54]. Meniscectomy is often accompanied by the onset of OA because of the high focal stresses imposed on articular cartilage and subchondral bone subsequent to excision of the meniscus. The studies that have explored the relationship between the meniscus and risk of disease progression in OA provide a clear indication of the risk inherent with damage to this vital tissue [55–57]. Each aspect of meniscal abnormality (whether change in position or damage) (Fig. 2.3) had a major effect on risk of cartilage loss in osteoarthritis.

Thus, the intact and functional meniscus is clearly important to the preservation of joint integrity and prevention of further joint damage. In contrast the meniscus plays a much smaller role in symptom genesis. An unfortunate consequence of the frequent use of MRI in clinical practice is the frequent detection of meniscal tears [58]. Degenerative lesions, described as horizontal cleavages, flap (oblique), or complex tears or meniscal maceration or destruction are associated with older age and are almost universal in persons with osteoarthritis [58]. In asymptomatic subjects with a mean age of 65 years, a tear was found in 67% using magnetic resonance imaging (MRI), whereas in patients with symptomatic knee OA, a meniscal tear was found in 91% [59]. In the interests of preserving menisci, an important cautionary note: meniscal tears are nearly universal in persons with knee OA and are unlikely to be a cause of increased symptoms [59, 60]. The penchant to remove menisci is to be avoided, unless there are symptoms of locking or extension blockade, at which point surgical treatment often becomes necessary [61].



**Fig. 2.3** Medial tibiofemoral osteoarthritis with extensive bone marrow lesions, attrition of the opposing articular surfaces and cartilage loss. In addition, a macerated meniscus has been extruded out of the medial compartment (*arrowhead*)

### The Role of Other Tissues

Periarticular muscles influence joint loading, and impairments in muscle function have been observed in people with OA [62]. Various studies have investigated the role of muscle strength on joint integrity, and some have explored the impact on physical functioning. Sharma et al. [63] conducted a 3-year longitudinal cohort study investigating factors contributing to poor physical functioning in 257 patients with knee OA. They found that in addition to factors such as age, reduced absolute quadriceps and hamstrings strength and poor proprioceptive acuity increased the likelihood of poor physical functioning as measured by the time to perform five repetitions of rising and sitting in a chair. In addition to their exploration in observational studies, there is ample evidence from clinical trials demonstrating that muscle strengthening exercises result in improvements in pain, physical function, and quality of life in people with knee OA [64, 65].

Obesity is the single most important risk factor for development of severe OA of the knee and more so than other potentially damaging factors including heredity [66]. Even if it is usually accepted that mechanical loading contributes to joint destruction in overweight patients, recent advances in the physiology of adipose tissue add further

insights in understanding the relationship between obesity and osteoarthritis. Indeed, the positive association between overweight or obesity and osteoarthritis is observed not only for knee joints but also for nonweight-bearing joints, such as hands [67, 68]. Furthermore, if weight loss may prevent the onset of osteoarthritis, the loss of body fat is more closely related to symptomatic benefit than is the loss of body weight [69]. Local fat depots may play an important role in disease and symptoms genesis. Among these tissues, the synovium and infrapatellar fat pad appear to produce large amounts of adipokines [70]. Until recently, the fat pad, which is an extra-synovial but an intra-articular tissue, had been neglected. However, this adipose tissue is able to release growth factors, cytokines and adipokines [43]. Since obese individuals have higher concentrations of inflammatory markers, inflammation may contribute to functional limitation and disease progression in those with OA [71]. Besides direct effects on the joint, inflammatory mediators can affect muscle function and lower the pain threshold.

Another source of joint pain in OA may be from the nerves themselves. Following joint injury in which there is ligamentous rupture, the nerves which reinnervate the healing soft tissues contain an overabundance of algogenic chemicals such as substance P and calcitonin gene-related peptide. An interesting observation of these new nerves was that their overall morphology was abnormal with fibers appearing punctate and disorganized [72, 73]. Since these phenomena are consistent with the innervation profiles described in nerve injury models, we speculate that injured joints may develop neuropathic pain post-trauma. Indeed, treatment of inflamed joints with the neuropathic pain analgesic gabapentin can also relieve arthritis pain [74].

### Conclusion

Though cartilage is aneural and avascular, it plays a central role in the pathophysiology of symptomatic OA, and cartilage abnormalities are directly associated with damage to other tissues within the joint that contain nociceptors. The pathophysiology of pain in OA is complex and similarly the symptomatic presentation in OA diverse and heterogeneous. Recent studies, particularly those with an emphasis on MRI, are providing unique insights into the relation between structure and symptom genesis. The traditional predominant focus of imaging studies and preclinical investigation is cartilage. However, the subchondral bone, periosteum, periarticular ligaments, periarticular muscle spasm, synovium, and joint capsule are all richly innervated and are the likely source of nociception in OA. Attention to the many modulating factors that alter the experience of pain may improve the way we treat this disease.

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