

# Osteoarthritis and Rheumatoid Arthritis 2012: Pathophysiology, Diagnosis, and Treatment



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## Introduction

Osteoarthritis (OA) and rheumatoid arthritis (RA) are two of the most common musculoskeletal conditions affecting individuals across the United States. Distinguished by cartilage degeneration and bony overgrowth, OA affects approximately 13.9% of adults who are  $\geq 25$  years of age.<sup>1</sup> The incidence of OA rises with age with estimates that OA affects 12.4 million adults  $\geq 65$  years of age.<sup>1</sup> OA occurs more frequently in women, particularly after reaching 50 years of age; women are also at greater risk for developing OA in the knee or hip.<sup>1</sup>

RA, unlike OA, is an autoimmune condition characterized by inflammation, usually in bilateral joints, and systemic features, such as fatigue or fever.<sup>2</sup> RA is estimated to affect 1.5 million adults.<sup>2</sup> RA sufferers are typically younger than those who develop OA, with RA occurring between 20 to 30 years of age, and the incidence peaking at 35 to 50 years of age.<sup>2,3</sup> The incidence of RA is higher in women<sup>2</sup> with a higher lifetime risk (3.6%) compared to men (1.7%).<sup>4</sup>

While there is no cure for OA or RA, treatments that slow or halt the progression of RA are available. Unfortunately, the same is not true for OA, where current pharmacologic treatment focuses on symptomatic relief. This article not only highlights the differences in the pathophysiology and diagnostic criteria for OA and RA, but also describes current and potentially new treatment options for these conditions.

## Pathophysiology

Although the primary manifestations of OA and RA involve the joints, the underlying pathophysiology of each condition is distinct.

### Osteoarthritis and cartilage degeneration

Normally, cartilage undergoes a remodeling process, stimulated by joint movement or use.<sup>5</sup> In OA, this process is altered by a combination of mechanical, cellular, and biochemical processes, resulting in abnormal reparation of cartilage and an increase in cartilage degradation<sup>5</sup> (Figure 1). OA is primarily characterized by progressive cartilage loss, accompanied by an increased thickness of the subchondral plate, osteophytes (new bone at joint margins) and subchondral bone cysts.<sup>6</sup> With disease progression, vascular invasion and further calcification of nearby articular cartilage may occur, leading to decreased thickness of articular cartilage and, over time, bone remodeling and enhanced cartilage deterioration.<sup>6</sup> The inflammation that occurs typically involves the periarticular tissues and is generally milder in severity compared to RA.<sup>5</sup>

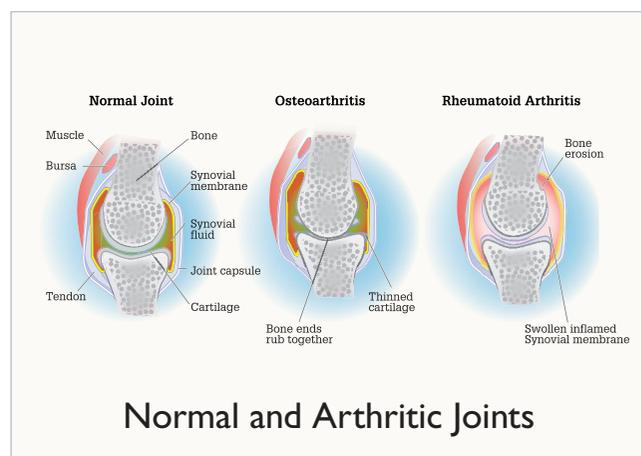
Osteoarthritis is associated with specific risk factors or causes including age, joint trauma, injury, or obesity.<sup>7</sup> Individuals

who are  $>50$  years of age are at a higher risk of developing OA.<sup>5</sup> The aging process has an impact on the cartilage extracellular matrix structure and components<sup>6</sup>; it is also associated with declining chondrocyte function and response rate to stimuli.<sup>5</sup> Joint injury and trauma, prolonged stress on the joint from sports activities or strenuous occupations, and joint overactivity, can increase an individual's risk over time.<sup>5</sup> Obesity increases the risk of OA, particularly in the weight-bearing joints.<sup>1,5</sup> With the growing number of both overweight and obese individuals, the incidence of OA and the number of hip and knee replacements is rising.<sup>8-10</sup> Genetics may also contribute to an increased risk.<sup>6</sup>

### Joint damage in rheumatoid arthritis

Unlike the pathophysiology of OA, which is largely mechanical, RA is an autoimmune disease. The initial triggers of RA are unclear; hormones, genetics and environmental factors may all play a role.<sup>2</sup> Once the initial immune response is triggered, cells of the immune system produce autoantibodies and inflammatory cytokines, creating a cascade of inflammation resulting in the formation of pannus; the pannus invades and destroys cartilage and bone. Additional joint damage and systemic complications ensue, resulting from a complex process of inflammatory mediators being released in the affected joint<sup>11</sup> (Figure 1).

Many factors impact the risk of developing RA. The risk of developing RA doubles with a first degree relative who has RA. There is also a hormonal relationship; RA is more common in females, and there are high rates of disease onset associated with pregnancy.<sup>2,11,12</sup> The impact of environmental stressors, especially smoking and chemical exposure (e.g., silicate), on genes is thought to drive the processes that induce autoimmune reactions leading up to the inflammation seen



**FIGURE 1.** Joint impact of osteoarthritis and rheumatoid arthritis

**TABLE 1. Summary of diagnostic criteria for osteoarthritis and rheumatoid arthritis**

Arthritis	Patient History	Physical Exam	Tests
Osteoarthritis	<ul style="list-style-type: none"> <li>• C/o palpable bony joint enlargement</li> <li>• Morning stiffness (lasting &lt;30 minutes)</li> <li>• Pain</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced range of motion</li> <li>• Joint malalignment</li> <li>• Crepitus</li> </ul>	<i>Radiologic</i> <ul style="list-style-type: none"> <li>• Presence of osteophytes</li> <li>• Joint space narrowing</li> </ul> <i>Laboratory</i> <ul style="list-style-type: none"> <li>• Clear synovial fluid</li> </ul>
Rheumatoid Arthritis	<ul style="list-style-type: none"> <li>• Pain duration <math>\geq 6</math> weeks</li> <li>• Morning stiffness (lasting &gt;30 minutes)</li> <li>• Systemic symptoms (e.g., fatigue, anorexia)</li> </ul>	<ul style="list-style-type: none"> <li>• Synovitis</li> <li>• Joint involvement, symmetrical</li> <li>• Joint destruction</li> <li>• Extra-articular manifestations</li> </ul>	<i>Radiologic</i> <ul style="list-style-type: none"> <li>• Erosions on X-ray or MRI</li> <li>• Synovitis noted by ultrasound or MRI</li> </ul> <i>Serology</i> <ul style="list-style-type: none"> <li>• ESR or C-reactive protein</li> <li>• Anti-CCP</li> <li>• Rheumatoid factor</li> </ul>

Sources: Singh et al.<sup>14</sup>; Altman et al.<sup>15</sup>; Aletaha et al.<sup>16</sup>

in RA.<sup>11,12</sup> Research estimates that a history of smoking can increase the relative risk of RA onset more than 2-fold, especially in individuals who are positive for anti-citrullinated protein antibodies (ACPA) or anti-cyclic citrullinated protein antibodies (anti-CCP); smoking is the strongest risk factor associated with RA.<sup>2</sup>

### Assessment of osteoarthritis and rheumatoid arthritis

#### Diagnosing osteoarthritis

The diagnosis of OA is based on patient history as well as the physical exam (*Table 1*). In advanced disease, radiologic signs of OA include asymmetrical narrowing of the joint space indicating loss of cartilage and/or the presence of osteophytes or bony overgrowth. The lack of radiologic evidence does not, however, rule out the presence of OA.<sup>5</sup> Joint aspiration is an invasive procedure and not required for diagnosis. However, if done, synovial fluid analysis may help confirm OA is non-inflammatory, with a white blood cell count <2000/mm<sup>3</sup>; it may also help rule in or out other conditions, such as gout or inflammatory arthritis.<sup>13</sup> Unlike RA, biologic markers are typically absent in OA patients.<sup>13</sup> OA symptoms tend to start on one side of the body initially and may include one or more joints.<sup>5</sup> The distal joints of the hands are most commonly affected as are the weight-bearing joints (e.g., knees, hips, cervical and lumbar spine).<sup>1</sup>

Morning stiffness is generally short-lived, usually lasting 30 minutes or less and may also occur with moderate activity<sup>5,13</sup>; pain is usually relieved by rest.<sup>13</sup> Other signs associated with OA typically involve joint tenderness, limited mobility, and local inflammation; systemic symptoms are usually absent.<sup>13</sup> Crepitus, a grating sensation between the joints, may also be present in later stages of the disease.<sup>13</sup>

#### Diagnosing rheumatoid arthritis

To diagnose RA, patient history is important. However, the physical exam, laboratory tests, radiographs, and other assessments (ie, functional status, disease activity) are frequently helpful in confirming a diagnosis (*Table 1*). RA usually affects multiple joints, although it may only affect a few sites during its initial presentation.<sup>11</sup> Contrary to OA, joint involvement in RA is typically symmetric and commonly affects small distal joints (ie, wrists, proximal interphalangeal joints, metacarpophalangeal joints).<sup>11</sup> Affected joints are usually tender, warm, and erythematous, with a “puffy” appearance, due to increased blood flow and synovial infiltration or synovitis from pannus formation.<sup>11</sup> This inflammation or pannus is generally palpable on physical exam as a “bogginess” or fullness over the joints.

Morning stiffness lasting >30 minutes is also a common sign of RA; the stiffness typically improves with movement.<sup>11</sup> Early symptoms of pain and stiffness in the joints, which may be accompanied by systemic features (e.g., anorexia, weakness, low-grade fever, fatigue), are recognized as the prodromal phase.<sup>11</sup> Assessment of the patient’s prognosis can impact treatment decisions. The American College of Rheumatology (ACR) recommendations for RA finds a poor prognosis can be inferred by one or more of the following features: functional limitations, presence of extra-articular manifestations (e.g., Felty’s syndrome, rheumatoid nodules, RA vasculitis), positive rheumatoid factor or anti-CCP antibodies; or radiographic evidence of bony erosions.<sup>14</sup>

#### Treatment and management strategies

Numerous treatment strategies are available to help improve patient functionality and mobility in both RA and OA.

Treatment for OA is mostly symptomatic whereas treatment for RA can slow down or prevent disease progression and joint destruction.

### Nonpharmacologic treatment options

Nonpharmacologic therapy plays an important role in the successful treatment of OA and RA.<sup>17,18</sup> Exercise, a key component of nonpharmacologic management, helps patients maintain mobility and function.<sup>18,19</sup> Both OA and RA guidelines recommend regular aerobic exercise<sup>18,19</sup>; RA patients, in particular, are urged to participate in strengthening exercises to maintain joint function, while non-weight bearing exercises (e.g., water aerobics) are highly recommended for OA patients.<sup>18,19</sup> Weight loss may also be suggested for patients with OA as a means to alleviate stress on weight-bearing joints.<sup>17,19-21</sup> Self management, including patient education and cognitive and behavioral therapy, can also help manage OA and RA symptoms and improve both social and self-care capabilities.<sup>19,21</sup>

OA guidelines recommend surgery in patients with extensively impaired function and pain that is refractory to medication therapy.<sup>17</sup> RA guidelines suggest surgery in patients experiencing intolerable pain due to joint destruction.<sup>18</sup>

### Acetaminophen

Acetaminophen, an effective option for mild-to-moderate pain, is the preferred first-line agent for the management of OA.<sup>19,22</sup> At recommended doses (less than 3000mg/day), acetaminophen is associated with fewer risks than non-steroidal anti-inflammatory drugs (NSAIDs), and can be effective at controlling OA pain.<sup>19</sup> Acetaminophen is hypothesized to work through the central nervous system, instead of the periphery, to inhibit prostaglandin synthesis.<sup>17</sup> If a patient does not have an adequate response to acetaminophen at an adequate dose and duration, topical or oral NSAIDs should be considered.<sup>19</sup>

### Non-steroidal anti-inflammatory drugs and COX-2 inhibitors

NSAIDs work by reducing production of pro-inflammatory and pain-related prostaglandins.<sup>17</sup> They inhibit two cyclooxygenase (COX) enzymes: COX-1 is important in the normal regulation of the gastrointestinal (GI) tract; COX-2 is up-regulated at sites of inflammation, among other functions, and may be responsible for inflammation.<sup>17</sup> Therefore, NSAIDs are effective in treating pain, immobility, and inflammation associated with OA.<sup>23</sup> As recommended by the ACR guidelines, initial RA treatment includes the use of NSAIDs (including selective COX-2 inhibitors) or salicylates. These treatment options neither alter RA progression nor protect

against joint damage and therefore, are used along with other medications.<sup>18</sup>

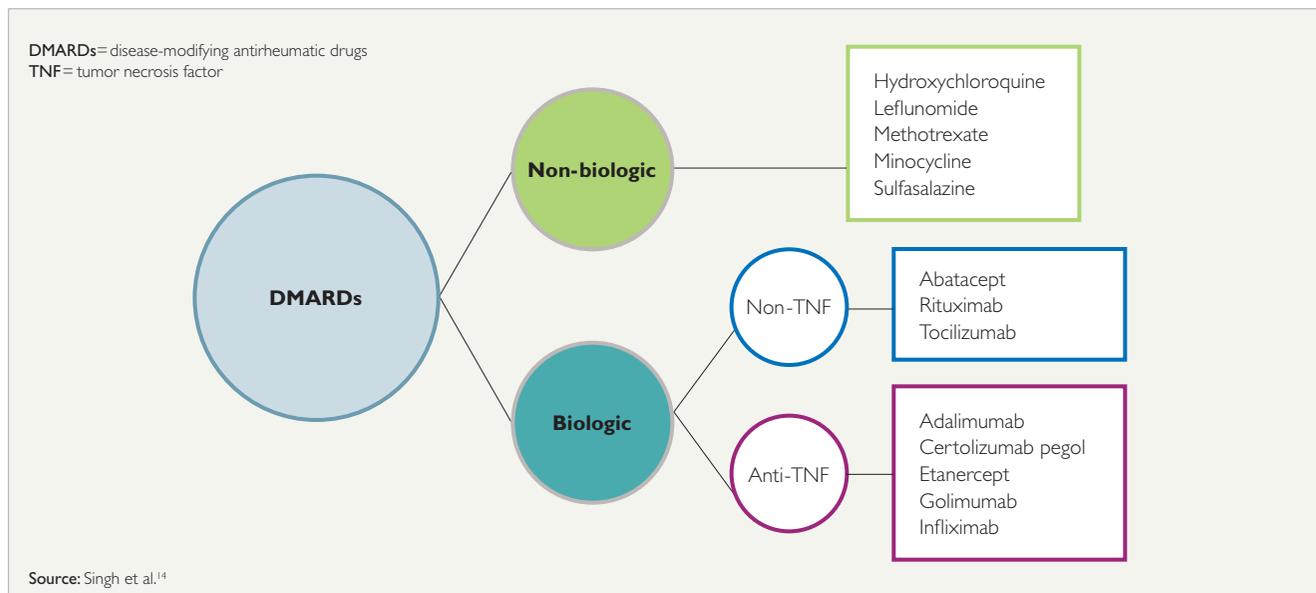
Adverse events associated with NSAIDs can have varying effects in the GI, cardiovascular, hepatic, and renal systems.<sup>23</sup> When managing patients with OA, the risk for adverse events increases with higher doses and longer treatment duration.<sup>23</sup> Characteristics that increase the risk of GI adverse events include prolonged NSAID use, history of GI disorders, heavy smoking or alcohol use, and concurrent use of aspirin, warfarin, or clopidogrel.<sup>23</sup> With the increased risk of adverse events with advanced age, topical NSAIDs may be preferred in patients who are  $\geq 75$  years of age, especially for patients with few joints involved.<sup>19</sup> RA patients, compared to OA patients, have an increased likelihood of experiencing adverse events, specifically gastroduodenal ulcers, with NSAID treatment. Patients at the highest risk of serious NSAID-associated ulcers include patients who have a history of ulcers, patients  $>75$  years of age, those taking high dose or multiple NSAIDs, and concomitant corticosteroids or anticoagulant use.

NSAIDs can be combined with a gastro-protectant agent (proton pump inhibitors (PPIs), histamine receptor antagonists (H<sub>2</sub>RAs), misoprostol) for patients who are at increased risk of GI adverse events.<sup>23</sup> Of those mentioned, PPIs may be the most effective overall.<sup>24</sup> PPIs have been found to be superior to H<sub>2</sub>RAs in preventing and healing GI events caused by NSAID use.<sup>24</sup> Although misoprostol, a prostaglandin analogue, has been found to be just as effective as PPIs,<sup>25</sup> GI adverse events (e.g., cramps, diarrhea) limit its use.<sup>24</sup> There are several formulations where the NSAID and the gastro-protectant are available as a combination (e.g., diclofenac sodium + misoprostol, ibuprofen + famotidine, naproxen + lansoprazole, naproxen + esomeprazole). These formulations may be useful in reducing the risk of GI adverse events and enhancing compliance.

### Glucocorticoids

If an OA patient fails NSAID therapy, intra-articular corticosteroid injections are another option.<sup>19</sup> Corticosteroid injections may provide pain relief over short-term periods (one to four weeks), but there is no evidence that these injections improve function.<sup>17</sup> Current ACR guidelines recommend the use of glucocorticoid injections for knee and hip OA if other pharmacologic therapies do not provide sufficient relief. The guidelines do not recommend corticosteroid injections in the treatment of hand OA.<sup>19</sup>

Low-dose oral glucocorticoids or local glucocorticoid injections are another treatment option for RA. These therapies are effective in relieving active RA symptoms (e.g., morning stiffness, joint pain, fatigue) in combination



**FIGURE 2.** DMARD categorization

with disease-modifying antirheumatic drugs (DMARDs).<sup>18</sup> They are frequently used as a short-term rescue medication or as a “bridge” therapy helping to control pain while a new DMARD is started. The lowest glucocorticoid dose (e.g.,  $\leq 5$ mg prednisone daily) should be prescribed, if appropriate. Delayed-release prednisone was approved by the Food and Drug Administration on July 2012 for use in RA patients. This formulation addresses the physiologic biorhythm of symptoms and was developed to help reduce joint symptoms upon awakening; it is intended to be taken at bedtime.<sup>26</sup>

Despite their efficacy, long-term low-dose oral glucocorticoid use can also cause several adverse events including hypertension, hyperglycemia, cataracts, osteoporosis, weight gain, fluid retention, and immunosuppression. For patients at high risk of osteoporotic fractures, ACR guidelines recommend maintaining adequate calcium and vitamin D intake, and to consider the use of a bone preserving agent.

Glucocorticoid injections may also be used to provide rapid and directed relief during RA flares.<sup>18</sup> For flares involving a small number of joints, glucocorticoid injections can provide effective symptom relief without medication regimen changes. No joint should be injected more than three times in one year; therefore, if more injections are required, other treatment options should be considered.<sup>18</sup>

#### Alternative to NSAIDs in osteoarthritis

Opioids should be reserved as a last option.<sup>19</sup> Tramadol may be effective in treating moderate-to-severe pain, however, for

individuals with severe pain who are unable to tolerate or do not respond to tramadol, opioid therapy should be considered. For patients who are not candidates for surgery, opioid therapy may also be considered.<sup>27</sup> Opioid therapy may be effective initially at reducing pain, but it is questionable whether or not the analgesic effect is sustained long-term.<sup>23</sup> Duloxetine is conditionally recommended by the ACR guidelines if other therapies are not effective. Hyaluronic acid injections are also recommended for patients who do not respond to pharmacologic and nonpharmacologic OA interventions; its use is limited to specific joints (e.g., knee).<sup>19</sup>

#### Disease-modifying antirheumatic drugs for rheumatoid arthritis

As a mainstay of RA pharmacotherapy, DMARDs are often utilized in combination with NSAIDs or glucocorticoids to decrease RA progression and maintain joint functionality.<sup>18</sup> DMARDs are classified as biologic or non-biologic agents; biologic DMARDs are further categorized as non-tumor necrosis factor (non-TNF) and anti-TNF agents (*Figure 2*) based on their mechanism of action.<sup>14</sup> The goal of using DMARDs in RA patients is to obtain medical remission or low disease activity.<sup>14</sup> Ideally, DMARD therapy should be started at disease onset, during early RA. Although therapy selection depends on RA severity, duration of symptoms, desired effects, toxicity, comorbidities, and administration requirements, it is important to know that treatment with DMARDs should be implemented at the onset of RA and can be adjusted at any stage.<sup>14</sup> For instance, RA patients may

**TABLE 2. Useful resources for patient information**

<p><b>Arthritis Foundation</b> www.arthritis.org</p>
<p><b>American College of Rheumatology</b> www.rheumatology.org</p>
<p><b>National Institute of Arthritis and Musculoskeletal and Skin Diseases</b> www.niams.nih.gov/Health_Info/Rheumatic_Disease/default.asp</p>
<p><b>National Institutes of Health</b> http://health.nih.gov/topic/Osteoarthritis http://health.nih.gov/topic/RheumatoidArthritis</p>

be prescribed methotrexate as monotherapy or in combination with a biologic DMARD, if their disease has either progressed or poor prognostic factors have evolved over the course of their disease. Therefore, referring patients suspected of having RA to rheumatology specialists is key to their management and helping prevent the development of irreversible joint destruction.<sup>14,18</sup>

### Novel options for rheumatoid arthritis

While many efficacious treatment options are currently available for RA patients, medications utilizing different mechanisms to treat RA are being developed which target specific inflammatory cytokines or cell signaling pathways. Tofacitinib is one novel oral biologic DMARD medication which has concluded phase III clinical trials and is currently being reviewed by the FDA for approval. Tofacitinib targets the Janus kinase (JAK) intracellular pathway.<sup>28</sup> Fostamatinib, an oral Syk inhibitor is also being investigated for RA. It is currently in a phase III clinical development program (OSKIRA) and its new drug application is expected to be filed with the FDA in 2013.<sup>29</sup>

### Conclusion

The differences between OA and RA, though both affect joints, exist in the pathophysiology, common symptoms, and diagnostic criteria; and reinforce the importance of understanding and correctly identifying these conditions. There is some overlap in management with the use of NSAIDs and glucocorticoids for OA and RA. The similarity ends there, as RA treatment with DMARDs continues to change disease outcomes. The clinician's role is to keep patients involved in the care of their arthritis. The self-care component of OA and RA treatment is aided by the useful information now available to patients on the internet. They can better manage their symptoms and improve their self-efficacy which ultimately leads to better outcomes (Table 2). ■

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